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Parenteral fluid regimens in the treatment of severe diarrhea in infants

Harris L. Smith, M.D., and James N. Etteldorf, M.D.*

MEMPHIS, TENN.

SINCE the description in 1926, by Powers[1] of his "comprehensive plan of treatment for the so-called intestinal intoxication of infants," a number of therapeutic regimens have been recommended for the treatment of severe diarrhea in infants. Notable among these regimens are those developed by Hartmann,[2] Darrow,[3, 4, 5] and Talbot and Butler.[6, 7] These differ in several respects, namely, in the composition of fluids employed, in the criteria for calculation of dosage, and in the routes by which various fluids are administered. Each of these treatment regimens has achieved results of merit. However, an objective comparison of these methods, or their modifications, is lacking in the literature. The present study was undertaken in order to provide clinical and laboratory data which would permit comparisons of three methods of therapy under similar conditions.

From the Pediatric Research Laboratory, Division of Pediatrics, College of Medicine, University of Tennessee, Memphis, and the Frank T. Tobey Memorial Children's Hospital, City of Memphis Hospitals, and the Le Bonheur Children's Hospital, Memphis, Tenn.

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**Address, Frank T. Tobey Memorial Children's Hospital, 860 Madison Ave., Memphis 3, Tenn.*

METHODS

For purposes of carrying out the study the following methods were chosen, and are outlined in Table I: (a) a modification of Hartmann's method,[2] (b) Butler and Talbot's method,[7] and (c) Darrow's method.[5] Efforts were made to evaluate the fluid therapy regi-

mens as to the effectiveness and rapidity of repair of abnormalities in fluid and electrolyte balance, the development of untoward effects, and the simplicity and safety of each method.

Modified Hartmann method. More than two decades ago, Hartmann and coworkers[9, 10] described the effectiveness of sodium racemic lactate over sodium bicarbonate for the relief of acidosis, and subsequently introduced a plan of therapy[2] which emphasized the use of this organic salt in liberal quantities.

In addition to its use during the early phase of treatment, one-sixth molar sodium r-lactate was mixed with hypotonic Ringer's solution ("fortified" lactated Ringer's solution) for subcutaneous administration during the later phases of treatment. Since 1945, Hartmann has included in his method of treatment the early feeding of a mixture of dextrose, Amigen, and a salt (D.A.S.) with a mineral composition, including potassium, which is similar to that of breast milk. In 1950, we modified Hartmann's method by increasing the quantity of potassium in the "fortified" lactated Ringer's solution to 19 mEq. per liter in an effort to supply the patients with more potassium during the early recovery phase and until they were able to retain oral feedings. We did not include oral administration of D.A.S. solution. An outline of our modification of Hartmann's method (Gaston method), as employed in this study, is given in Table I. The composition of fluids used in this and the other methods of treatment described herein is shown in Table II.

Darrow's method. In 1946, Govan and Darrow[3] described a therapeutic regimen based on measurements of the retention of water, sodium, potassium, and chloride during recovery from severe diarrhea. This method, as originally described by Darrow, utilizes half-isotonic saline with glucose as the initial hydration solution, followed by blood or plasma in severe cases. After these measures and the establishment of urinary flow, potassium lactate solution (Darrow's solution) is administered by the subcutaneous route, and glucose in water solution is given intravenously, as shown in Table II. In Darrow's method, the criteria for dosage was based on body weight for electrolyte-containing solutions, and the total fluid intake, on the number of calories metabolized.

Butler-Talbot method. As a result of their studies of the magnitude of requirements of normal infants and losses incident to diarrhea,[11] Talbot, Crawford, and Butler[6] were able to delineate in terms of surface area certain homeostatic limits for the administration of fluid and electrolytes. On the basis of their observations, a plan of therapy was devised for use in diverse types of fluid and electrolyte imbalances. This plan of therapy utilizes a dilute saline with glucose for initial hydration, followed by a hypotonic multiple electrolyte solution, as shown in Table I.

Table I. Summary of methods of parenteral fluid therapy

Group	*Hydration phase (First 90 minutes)*	*Reparative phase*		
		First day	*Second day*	*Third day*
Group I (modified Hartmann)	M/6 lactate 30 ml./Kg.	Lactated KCl Ringer's solution—70 ml./Kg. 5% glucose in distilled water—100 ml./Kg.	Lactated KCl Ringer's solution—50 ml./Kg. 5% glucose in distilled water—80 ml./Kg.	Lactated KCl Ringer's solution—40 ml./Kg. 5% glucose in distilled water—60 ml./Kg.
Group II (Butler-Talbot)	0.33 NaCl with 5% dextrose 450 ml./M.^{2}	Talbot's (No. 75) solution—3,000 ml./M.^{2}	Talbot's (No. 75) solution—2,400 ml./M.^{2}	Talbot's (No. 75) solution—1,500 ml./M.^{2}
Group III (Darrow)	5% dextrose with half-isotonic saline 30 ml./Kg.	Darrow's (K-lactate) solution—80 ml./Kg. 5% glucose in distilled water—100 ml./Kg.	Darrow's (K-lactate) solution—60 ml./Kg. 5% glucose in distilled water—80 ml./Kg.	Darrow's (K-lactate) solution—40 ml./Kg. 5% glucose in distilled water—60 ml./Kg.

Table II. Electrolyte composition of individual and combined parenteral fluids

Fluid	*Na (mEq./L.)*	*K (mEq./L.)*	*Ca (mEq./L.)*	*Cl (mEq./L.)*	*Lactate (mEq./L.)*	*HPO_4 (mEq./L.)*	*Cations + anions (mOsm./L.)*	*CHO (Gm./L.)*
M/6 sodium r-lactate	167				167		234	
Lactated KCl Ringer's solution	135	17	2	82	72		307	
5% glucose in distilled water								50
0.33% NaCl with 5% dextrose	51			51			102	50
Talbot's (No. 75) solution	40	35		40	20	15	142.5	50
Half-strength saline	77			77			154	
Darrow's (K-lactate) solution	122	35		104	53		314	
First 24 hours' fluids, if pooled:								
Group I (modified Hartmann)	72	6	1	29	50	0	157.5	25
Group II (Butler-Talbot)	42	30		42	17	13	137.5	50
Group III (Darrow)	55	13		50	20	0	140	31

The dosage criterion is surface area, and the intravenous route of administration is used exclusively.

Points of difference and similarity. In order to facilitate comparison of the quantities of the various ingredients of each of the regimens during the first day of treatment, calculations were made in the hypothetical case of an infant whose body weight is 5 kilograms and whose surface area is 0.29 square meters.[12] These values are shown in Table III and represent a summation of all the constituents of the parenteral fluids used in each method. From these calculations, and from Tables I and II, a number of similarities and differences between the three plans of therapy are apparent. Although the osmolarity of the individual solutions differs, the osmolar concentrations of the solutions, if pooled, are similar in each method of treatment with respect to electrolytes. The amount of total water and free water provided in each regimen is also approximately the same in each method. The carbohydrate supplied, although adequate in all three regimens, is much greater in the Butler-Talbot plan. The sodium provided by the modified Hartmann plan is slightly greater than that of Darrow's method and almost twice as great as that of the Butler-Talbot method. The amount of potassium provided by the latter greatly exceeds that provided by the modified Hartmann regimen. Darrow's method provides an intermediary quantity of potassium. The chloride supplied by Darrow's method and, to a lesser degree, by the Butler-Talbot method is much higher than that in the modified Hartmann method. The reverse is true with regard to lactate. Phosphate is included in the Butler-Talbot regimen but is absent in the other plans of treatment. Calcium, in small quantities, is included only in the modified Hartmann regimen. Patients of all groups received parenteral fluid therapy for 2 days. In 3 cases each of Groups I and II, and in 1 case of Group III, parenteral fluid therapy was required through the third hospital day.

CLINICAL MATERIAL AND METHODS

Patients. Fifty-three infants, all less than 15 months of age and suffering from severe diarrhea, were included in this study. During the early phase of the study, 13 patients were assigned alternately to Groups I and II. The other patients were assigned in rotation to Groups I, II, and III. Group I was treated by means of the modified Hartmann method, Group II by the Butler-Talbot method, and Group III by the Darrow method. Patients with abnormalities of homeostatic mechanisms were excluded from the study. Infusions of blood or plasma were not used in conjunction with any of the three methods of

Table III. Comparison of quantities of water, electrolytes, and carbohydrate provided during first day of fluids used during initial hydration and reparative periods)

Group	*Water*		*Sodium*		*Potassium*	
	ml./Kg.	*ml./M.²*	*mEq./Kg.*	*mEq./M.²*	*mEq./Kg.*	*mEq./M.²*
I (modified Hartmann)	200	3,450	14.0	248	1.4	24
II (Butler-Talbot)	200	3,450	8.4	141	6.0	103
III (Darrow)	210	3,620	12.0	209	2.8	48

fluid therapy studied. All patients were confined to an air-conditioned ward during the course of treatment and observation. A strictly uniform schedule was followed in reinstitution of oral feedings. After a period of 18 hours of fasting, the patients were offered 5 per cent glucose in water for 12 hours. For the remainder of the study period, diets were altered to include a formula which consisted of equal amounts of skimmed milk and water with carbohydrate added to make a 5 per cent mixture. Toward the end of the study period the patients were offered in sequence mixtures of skimmed milk and water, and of homogenized milk and water. These formulas also had a 5 per cent carbohydrate content. Oral intake of fluid during the study period was measured and found to be comparable in all three treatment groups. Stool cultures were positive for Salmonella or Shigella in 15 per cent of Groups I and III, and in 11 per cent of Group II.

Collection of blood samples. Samples of blood were collected under oil in heparinized syringes. The electrolyte concentration of the heparin used was determined to be negligible. Samples were collected before treatment, at 12, at 36, and at 60 hours after initiation of treatment. Determinations of blood pH were performed at the patient's bedside immediately after each sample was obtained. The remainder of each sample was centrifuged at 3,500 r.p.m. for 30 minutes. The plasma was then transferred under oil to a separate tube. If evidence of hemolysis was detected, the sample was discarded and another obtained. The analyses of plasma were usually performed shortly after its separation from the blood cells. In the event of an occasional delay the samples were stored in tightly stoppered plastic tubes at 40° F.

Laboratory methods. In addition to determinations of blood pH, analyses were made for plasma carbon-dioxide content, sodium, potassium, and chloride. Hemoglobin, hematocrit, total and differential blood counts were performed on samples of capillary blood taken before treatment and 60 hours later. Determinations of blood pH were made by means of a Beckman pH meter, Model G. The classic method of Van Slyke was utilized for the analyses of plasma carbon-dioxide content. Determinations of sodium and potassium were made by means of a Beckman direct-reading flame photometer, Model 41. In our laboratory, the values considered to be normal during infancy are: pH = 7.35 to 7.45, carbon-dioxide content = 20 to 29 mEq./L., sodium = 135 to 150 mEq./L., and potassium = 3.8 to 5.4 mEq./L.

RESULTS

Comparison of clinical observations. The clinical status of patients was recorded at frequent intervals during the course of treatment. In addition to careful observations relative to the severity of the diarrhea, attention was directed toward evaluation of the state of hydration, respiratory patterns, and presence or absence of disturbances of the central nervous system.

The state of hydration, as evidenced by improved skin turgor, increased moisture of mucous membranes, return of fullness of fontanels, appearance of the eyes, and increase in body weight, was comparable in all three groups of patients during the course of treatment. With the exception of 3 patients in each of Groups I and II, and 1 patient of

day of treatment, calculated on basis of body weight and surface area (including

Chloride		Lactate		Phosphate		Carbohydrate		Calories	
mEq./Kg.	mEq./M.²	mEq./Kg.	mEq./M.²	mEq./Kg.	mEq./M.²	Gm./Kg.	Gm./M.²	per Kg.	per M.²
5.8	100	10.0	172	0.0	0	5.0	86	20	344
8.4	141	3.4	58	2.6	45	10.0	172	40	688
10.7	184	4.2	73	0.0	0	6.5	112	26	412

Group III, parenteral fluid therapy was not required after the first 48 hours of treatment. The patients who required parenteral fluid therapy beyond 48 hours of hospitalization sustained severe concurrent losses of fluid and electrolytes during treatment.

Edema developed during treatment in 3 patients of Group I, and in 1 patient of Group III. It is interesting that all 4 of these infants had elevated levels of plasma sodium when edema was present. Conversely, 5 patients of Group I, and 1 patient of Group III were hypernatremic at the end of 36 to 40 hours of treatment but were not edematous. No edema developed in the subjects of Group II.

Kussmaul respiratory patterns were present before treatment in 16, 15, and 11 patients, respectively, of Groups I, II, and III. These patterns persisted for the shortest period of time in the patients of Group I. In this group, the maximum duration of Kussmaul respiration was 3 hours after initiation of treatment, and in most cases was undetectable after 2 hours. In Group II, half of the subjects continued to exhibit patterns of deep, pauseless respiration for a period of 12 hours or longer. The duration of this sign in Group III was intermediate to that in the other two groups, with an average of 6 hours. Because of persistent Kussmaul respiration in 2 infants of Group II for 24 hours the treatment was altered temporarily by the administration, intravenously, of one-sixth molar sodium r-lactate, 30 ml. per kilogram. The blood pH of these infants had failed to rise above 7.10 before interruption of their plan of therapy. Two hours after the infusion of sodium r-lactate, Kussmaul respiratory patterns were not present and the blood pH values were 7.27 and 7.29, respectively. In the patients of this study, Kussmaul respiratory patterns were uniformly associated with blood pH values below 7.25. The infusion of one-sixth molar sodium r-lactate, 30 ml. per kilogram, regularly produced increments in blood pH which averaged 0.2 pH units 2 hours after the infusion. The influence of the various methods of treatment on blood pH will be discussed more completely later.

Neurological manifestations were not limited to any one of the three groups of patients. In all groups, lethargy and apathy were prominent features in the infants whose pretreatment values of plasma sodium were normal or subnormal. These manifestations were most pronounced in the patients whose stool cultures were positive for Salmonella or Shigella. In contrast to these infants, 50 per cent of those with hypernatremia were continuously hyperirritable and showed signs of meningeal irritation. Paresis of cranial or peripheral nerves did not occur in any of the infants studied. The only patient who exhibited convulsive seizures during the course of observations was an infant of Group I whose plasma sodium was normal before treatment and remained so during treatment. Lumbar puncture was performed in this patient and in all patients who showed hyperirritability and/or signs suggestive of meningeal irritation. The studies of cerebrospinal fluid, which did not include determinations of electrolytes or osmolarity, were normal with respect to cell counts, culture, and determination of protein and sugar.

The use of the intravenous route as the sole route for the administration of parenteral fluid, as used in Group II, appeared to be much more desirable than the use of in-

Table IV. Comparison of blood pH

	Group I (modified Hartmann)	*Group II (Butler-Talbot)*	*Group III (Darrow)*
Before treatment.			
Range	6.98-7.30	7.01-7.31	7.08-7.30
Mean	7.13	7.16	7.15
	(20)	(19)	(7)
Between 7.35-7.45	0%	0%	0%
Below 7.35	100%	100%	100%
	(20)	(19)	(7)
Above 7.45	0%	0%	0%
12-16 hours.			
Range	7.20-7.55	7.02-7.41	7.26-7.42
Mean	7.38	7.24	7.34
	(20)	(19)	(7)
Between 7.35-7.45	35%	16%	30%
	(7)	(3)	(2)
Below 7.35	45%	84%	70%
	(9)	(16)	(5)
Above 7.45	20%	0%	0%
	(4)		
36-40 hours.			
Range	7.28-7.54	7.26-7.45	7.36-7.45
Mean	7.42	7.36	7.40
	(20)	(18)	(7)
Between 7.35-7.45	60%	55%	100%
	(12)	(10)	(7)
Below 7.35	10%	45%	0%
	(2)	(8)	
Above 7.45	30%	0%	0%
	(6)		
60-64 hours.			
Range	7.35-7.52	7.34-7.44	7.35-7.40
Mean	7.43	7.41	7.39
	(20)	(17)	(7)
Between 7.35-7.45	65%	88%	100%
	(13)	(15)	(7)
Below 7.35	0%	12%	0%
		(2)	
Above 7.45	35%	0%	0%
	(7)		

travenous and subcutaneous routes simultaneously. Since the introduction of microdrip and Gardner-Murphy infusion sets, technical problems encountered in venipuncture and hazards such as the overloading of the circulatory system with excessive fluid volume and the production of toxic levels of plasma potassium may be easily avoided.

Comparison of blood chemical observations.

Blood pH. All patients studied showed a marked acidemia. Pretreatment values of blood pH ranged from 6.98 to 7.30 (mean 7.13), 7.01 to 7.31 (mean 7.16), and 7.08 to 7.30 (mean 7.15), respectively, in Groups I, II, and III. The changes in blood pH observed during treatment are summarized in Table IV. From this table it will be noted that, in contrast to the other two groups, relatively few of the infants of Group II achieved normal values of blood pH in less than 36 to 40 hours of treatment. Eighty-four per cent of this group had subnormal values at 12 to 16 hours, and 45 per cent continued to have low levels of blood pH at 36 to 40 hours. Final observations, made 60 to 64

hours after initiation of treatment, showed persistently low levels of pH in 2 patients of the group. In Group I, levels of blood pH rose much more rapidly to normal, and in a relatively high percentage of patients became elevated above 7.45. At 12 to 16 hours, 7 patients (35 per cent) of the group had already achieved normal levels of pH, and 4 (20 per cent) had exceeded the normal range. In the other 9 patients (45 per cent), despite definite increments in pH, the values remained below pH 7.35. At the next sampling period, only 2 infants had low values of pH, but 6 (30 per cent) had developed levels of pH above 7.45 which were unaccompanied by visible clinical disturbances. This tendency toward alkalemia continued and increased slightly during the remainder of the observation period, with 7 patients continuing to exhibit abnormally high levels of blood pH. In Group III the percentage of patients with normal pH values at 12 to 16 hours after initiation of treatment was comparable to that in Group I. Although 70 per cent of these infants continued to be acidemic at this time, none developed levels of pH

Table V. Comparison of plasma CO_2 content

	Group I (modified Hartmann)	*Group II (Butler-Talbot)*	*Group III (Darrow)*
Before treatment.			
Range	4.0-16.7	6.3-17.0	6.0-15.0
Mean	9.1	10.0	11.5
	(20)	(19)	(13)
Between 20-29 mEq./L.	0%	0%	0%
Below 20 mEq./L.	100%	100%	100%
	(20)	(19)	(13)
Above 29 mEq./L.	0%	0%	0%
12-16 hours.			
Range	11.1-35.3	8.6-20.9	14.0-21.2
Mean	20.4	14.4	17.7
	(20)	(18)	(13)
Between 20-29 mEq./L.	35%	11%	31%
	(7)	(2)	(4)
Below 20 mEq./L.	50%	89%	69%
	(10)	(16)	(9)
Above 29 mEq./L.	15%	0%	0%
	(3)		
36-40 hours.			
Range	18.9-38.0	10.0-24.3	17.0-25.1
Mean	25.4	18.2	21.0
	(19)	(17)	(12)
Between 20-29 mEq./L.	53%	47%	75%
	(10)	(8)	(8)
Below 20 mEq./L.	15%	53%	25%
	(3)	(9)	(4)
Above 29 mEq./L.	32%	0%	0%
	(6)		
60-64 hours.			
Range	20.5-38.0	16.4-29.9	20.0-27.9
Mean	25.4	22.6	23.3
	(19)	(16)	(13)
Between 20-29 mEq./L.	68%	88%	100%
	(13)	(14)	(13)
Below 20 mEq./L.	0%	12%	0%
		(2)	
Above 29 mEq./L.	32%	0%	0%
	(6)		

Table VI. Comparison of levels of plasma sodium

	Group I (modified Hartmann)	*Group II (Butler-Talbot)*	*Group III (Darrow)*
Before treatment.			
Range	130-186	122-194	122-194
Mean	145	147	147
	(20)	(19)	(12)
Between 135-150 mEq./L.	50%	63%	58%
	(10)	(12)	(7)
Below 135 mEq./L.	30%	21%	17%
	(6)	(4)	(2)
Above 150 mEq./L.	20%	16%	25%
	(4)	(3)	(3)
12-16 hours.			
Range	130-196	120-168	129-155
Mean	146	141	144
	(20)	(19)	(12)
Between 135-150 mEq./L.	65%	37%	77%
	(13)	(7)	(9)
Below 135 mEq./L.	10%	47%	6%
	(2)	(9)	(1)
Above 150 mEq./L.	25%	16%	17%
	(5)	(3)	(2)
36-40 hours.			
Range	135-186	126-160	136-181
Mean	150	142	145
	(20)	(18)	(13)
Between 135-150 mEq./L.	60%	44%	84%
	(12)	(8)	(11)
Below 135 mEq./L.	0%	39%	0%
		(7)	
Above 150 mEq./L.	40%	17%	16%
	(8)	(3)	(2)
60-64hours.			
Range	138-172	130-163	136-170
Mean	148	142	141
	(20)	(17)	(12)
Between 135-150 mEq./L.	75%	70%	92%
	(15)	(12)	(11)
Below 135 mEq./L.	0%	24%	0%
		(4)	
Above 150 mEq./L.	25%	6%	8%
	(5)	(1)	(1)

above 7.45. During the subsequent periods of observation, the pH of all patients of this group was normal.

Plasma bicarbonate. All patients studied had uncompensated metabolic acidosis. As shown in Table V, carbon-dioxide content ranged from 4 to 17 mEq. per liter in the various groups before treatment. Mean values were 9.1, 11.5, and 10.0 mEq. per liter, respectively, in Groups I, II, and III. A definite parallelism between values of plasma bicarbonate and blood pH was evident throughout the investigation. Thus, the tendency toward development of high levels of bicarbonate in Group I and the persistence of low levels of bicarbonate in Group II was noted. In Group I, 7 patients (35 per cent) had reached normal levels of bicarbonate by 12 to 16 hours, and 15 per cent had already exceeded 29 mEq. per liter. This same tendency continued to be evident at 36 to 40 hours and at 60 to 64 hours, with an incidence of normal values in 60 to 65 per cent of the patients, whereas the remainder

Table VII. Comparison of levels of plasma potassium

	Group I (modified Hartmann)	*Group II (Butler-Talbot)*	*Group III (Darrow)*
Before treatment.			
Range	2.0-8.2	2.9-7.3	3.0-7.3
Mean	4.9	4.8	4.7
	(20)	(19)	(12)
Between 3.8-5.4 mEq./L.	50%	26%	75%
	(10)	(5)	(9)
Below 3.8 mEq./L.	10%	21%	8%
	(2)	(4)	(1)
Above 5.4 mEq./L.	40%	53%	17%
	(8)	(10)	(2)
12-16 hours.			
Range	1.8-5.8	3.7-8.0	3.3-4.7
Mean	3.6	5.7	3.9
	(20)	(19)	(12)
Between 3.8-5.4 mEq./L.	35%	55%	83%
	(7)	(10)	(10)
Below 3.8 mEq./L.	60%	5%	17%
	(12)	(1)	(2)
Above 5.4 mEq./L.	5%	40%	0%
	(1)	(8)	
36-40 hours.			
Range	2.0-5.2	4.2-7.6	3.9-5.9
Mean	3.8	5.5	4.6
	(20)	(18)	(13)
Between 3.8-5.4 mEq./L.	55%	62%	85%
	(11)	(11)	(11)
Below 3.8 mEq./L.	45%	0%	0%
	(9)		
Above 5.4 mEq./L.	0%	38%	15%
		(7)	(2)
60-64 hours.			
Range	2.5-5.6	4.0-7.3	4.0-6.1
Mean	4.1	5.5	4.8
	(20)	(17)	(13)
Between 3.8-5.4 mEq./L.	75%	65%	85%
	(15)	(11)	(11)
Below 3.8 mEq./L.	25%	0%	0%
	(5)		
Above 5.4 mEq./L.	0%	35%	15%
		(6)	(2)

showed abnormally high levels of bicarbonate. Low levels for base bicarbonate persisted in 16 of the 19 infants of Group II beyond the first 12 to 16 hours of observation. Subnormal levels continued in 9 (53 per cent) of this group beyond 36 to 40 hours of treatment and were still evident in 2 infants at the time of the final sampling at 60 to 64 hours. Groups II and III showed no tendency to overshoot the normal range of plasma bicarbonate. Although 9 (69 per cent) of the infants of Group III continued to exhibit subnormal values of bicarbonate after 12 to 16 hours of treatment, none had abnormally low values during the remainder of the observation periods.

Plasma sodium. Pretreatment values of plasma sodium ranged from 130 to 186 mEq./L. (mean 145) in Group I, and from 122 to 194 mEq./L. (mean 147) in Groups II and III, as shown in Table VI. Values for sodium below 135 mEq./L. were present in 30, 21, and 17 per cent of the infants in Groups I, II, and III, respectively. Levels

above 150 mEq./L. occurred before treatment in 4 infants of Group I, and in 3 infants each of Groups II and III. We were able to predict elevated levels of sodium in 50 per cent of these patients on the basis of skin turgor, manifestations in the central nervous system, and dryness of mucous membranes out of proportion to subcutaneous dehydration. Values of plasma sodium remained elevated throughout the course of treatment in all of the infants of the study who were hypernatremic prior to treatment, regardless of the therapeutic regimen employed. In Group I, 4 infants whose levels of plasma sodium were normal before institution of therapy developed hypernatremia during observation, so that at 36 to 40 hours the incidence of hypernatremia was appreciably increased in this group. The high values for sodium were correlated with elevated values for blood pH and plasma bicarbonate. Similar tendencies toward elevated levels of sodium were not evident in the other groups in our studies. On the contrary, the incidence of hyponatremia in Group II increased to 47 per cent during the early period of observation and had dropped only to 24 per cent after 60 to 64 hours. The subnormal pretreatment values of sodium of patients of Groups I and III were rapidly repaired during the early phases of treatment, so that none of them were hyponatremic at 36 to 40 and at 60 to 64 hours. In no instance did patients of Groups I and III develop subnormal levels of sodium during therapy.

Plasma potassium. Observations on levels of plasma potassium before and during treatment are summarized in Table VII. From this table it may be seen that the incidence of normal pretreatment levels of plasma potassium varied considerably among the three groups studied, and the unpredictability of levels of plasma potassium is demonstrated. Thus, only 26 per cent of the patients of Group II had levels between 3.8 and 5.4 mEq. per liter; the majority (53 per cent) of the group had elevated values, and the other 4 infants had subnormal values. In Groups I and III, elevated levels of potassium occurred in 40 and 17 per cent of the patients, respectively, and low levels were present in only 2 infants of Group I and 1 infant of Group III. At 12 to 16 hours, a markedly increased incidence of hypokalemia occurred in Group I, the group receiving parenteral fluids containing the greatest amounts of sodium r-lactate and the smallest amounts of potassium. This tendency to develop hypokalemia remained quite noticeable throughout the remainder of the period of observation. At the time of the final sampling, 25 per cent of this group maintained subnormal levels, and the mean value, 4.1 mEq. per liter, hovered near the lower limit of the normal range.

When the blood pH, plasma base bicarbonate, and potassium are considered simultaneously, the relationship between alkalemia and hypokalemia is evident. Furthermore, with the administration of small quantities of base bicarbonate along with high amounts of potassium, one observes the correlation between elevated levels of potassium and acidemia. These phenomena are clearly demonstrated in Groups I and II, respectively.

In our experience, levels of plasma potassium below 3 mEq. per liter are frequently associated with signs and symptoms of hypokalemia, and we are at a loss to explain the lack of these findings in the 2 profoundly hypokalemic infants of Group I. Serial electrocardiographic tracings were not obtained for any of the infants included in our study. Infants of Group II, whose incidence of elevated pretreatment levels of potassium was greatest and whose treatment regimen provided the largest quantities of potassium, showed a tendency toward persistence of high levels of plasma potassium. Although the incidence of hyperkalemia gradually declined during the 64 hour period of observation, the final determinations revealed that levels of potassium remained above normal in 35 per cent of the cases. Clinical symptoms and signs of potassium toxicity could not be correlated with these elevated levels of plasma potassium, even though a peak of 8 mEq. per liter was reached in 1 of the patients. Although restoration of normal levels of plasma potassium was effectively

accomplished in the infants of both Groups II and III, the incidence of hyperkalemia in Group II was considerably greater than in Group III.

DISCUSSION

Our findings indicate that the modified Hartmann method is the most effective of the three methods evaluated with regard to promptness of relief of acidosis and acidemia. The effects of sodium r-lactate on levels of plasma bicarbonate and blood pH, as demonstrated in the present study, are similar to the observations of Hartmann and Senn.[13] These investigators have also shown that the amounts of sodium bicarbonate or sodium r-lactate necessary to restore the normal concentration of bicarbonate in plasma are often greater than the amount of sodium bicarbonate present in the extracellular fluid. This may be due to any one of the mechanisms which regulate the distribution of sodium, as mentioned above.

Observations during the reparative phase of therapy with the modified Hartmann regimen indicated that the normal range of blood pH is frequently exceeded because of the quantities of sodium r-lactate which were administered in the absence of adequate potassium. This tendency of sixth molar sodium r-lactate to foster the development of alkalosis, along with the added disadvantages of promoting hypernatremia and aggravating potassium deficits, has been previously pointed out by Kelsey.[14] We believe that the advantages inherent in its *judicious use,* both in hydrating and reparative solutions, outweigh the disadvantages, especially when an adequate quantity of potassium is simultaneously provided in the reparative phase of treatment. As will be mentioned subsequently, we also believe that the modified Hartmann method of treatment, as employed in the present investigation, failed to supply adequate quantities of potassium, and that by providing this cation in greater quantities, less sodium r-lactate would have been required. Although transient alkalosis and alkalemia of moderate degree did not appear to be detrimental from a clinical standpoint, the occurrence of these biochemical disturbances during therapy are undesirable. Indeed, the goal of parenteral fluid therapy is the achievement of the normal state of homeostasis without wide fluctuations in cation-anion levels. The high incidence of occurrence of hypokalemia during therapy with the modified Hartmann regimen, despite early institution of oral feedings, emphasizes the inadequacy of the modified Hartmann method in correcting severe deficits of potassium.

On the basis of the observations in this and subsequent investigations, we have further modified our modification of Hartmann's method of therapy in an effort to prevent the tendencies toward an excess of base bicarbonate, alkalemia, and potentiation of deficits of potassium. These modifications, which will be more fully described in a subsequent paper, include the use of a twelfth molar sodium racemic lactate solution which contains 5 per cent dextrose as the initial hydrating solution, and the revision of the composition of the multiple electrolyte solution to contain more liberal amounts of potassium and less sodium. As presently used, the composition of the multiple electrolyte solution in milliequivalents per liter is: sodium 122, potassium 30, calcium 2, chloride 69, and lactate 85.

The prolonged acidosis and acidemia observed in infants subjected to the Butler-Talbot regimen was disturbing to us. Although the dynamics of acid-base balance are inseparable from those of the total ionic structure of the body fluids, it is our belief that special attention should be directed, earlier, toward correction of acid-base imbalance before multiple electrolyte reparative solutions are provided. Unfortunately, data are not available which clearly delineate the rapidity or the magnitude of incrementation of pH which is desirable in extremely acidotic infants. Although the physiologic effects of moderately low values of pH have not been clearly elucidated, the devastating effects of extremely low blood pH on various intracellular and extracellular processes are undeniable. Permeability of cell membranes

and/or integrity of cell walls which lead to abnormal transfers of ions in and out of cells, as well as cellular breakdown, constitutes one of the principal threats of severe acidemia.[15] Vital enzymatic processes, such as those concerned with utilization of carbohydrate[16] and oxygen,[17] are also profoundly influenced by sharp decrements in the pH of body fluids. It is generally accepted that transmission of nerve impulses, as well as balance between ions of body fluids, depends upon maintenance of pH within narrow limits. Alterations in cerebral electrical activity have been observed during fluctuations in blood carbon-dioxide tension.[18] The foregoing observations emphasize the importance of re-establishing normal acid-base equilibrium as rapidly as possible in states of severe acidemia, especially during infancy when growth and development are progressing so rapidly.

Although levels of plasma sodium may be normal, depressed, or elevated in association with diarrhea, total body deficits of sodium occur with regularity. In our experience,[19] and in that of Gamble and co-workers,[20] hypertonic dehydration occurs concomitantly with diarrhea much less frequently than does hypotonic dehydration. In the present study, infants with hypertonic dehydration responded in a similar manner, from both clinical and biochemical viewpoints, regardless of the method of treatment employed. The infusion of one-sixth molar sodium r-lactate, as used in the hydrating phase of the modified Hartmann method, did not appear to be detrimental to patients with hypertonic dehydration. These observations are in accord with those of Kerrigan.[21] On the other hand, no adverse effects were associated with the use of hypotonic saline hydrating solutions as used in Groups II and III.

Infants treated by the Butler-Talbot method tended to maintain low levels of plasma sodium, and, in some instances, showed further decrements in these levels. This high incidence of hyponatremia in this group during the first 2 days of observation raises the question of the efficacy of this method in the repair of large deficits of sodium. Although the multiple electrolyte solution of the Butler-Talbot method provides greater quantities of sodium than were present in a previously described solution,[22] additional sodium, within limits of tolerance, might increase the usefulness of this method without an overload of sodium.

The repair of potassium deficits was effectively achieved by means of either the Butler-Talbot method or the Darrow method. In the infants treated by the Butler-Talbot method, low levels of plasma potassium were promptly returned to normal and rather frequently reached levels above the normal range. Although a level of 8 mEq. per liter was attained in one instance, no clinical evidence of hyperkalemia developed. Elevated pretreatment levels of potassium in infants treated by the Butler-Talbot method tended to persist during treatment and were probably more closely related to the prolonged acidemia than to the quantities of potassium being infused, since adequate urinary flow was present. The effects of moderately elevated levels of plasma (5.4 to 7.0 mEq. per liter) which are frequently observed during acidemia have not been clearly delineated. Concentrations of plasma potassium have been shown to vary inversely with plasma pH.[23, 24, 25] Burnell and Scribner[26] state that decrements of 0.1 unit in pH of the extracellular fluid result in an increase of 0.4 to 1.2 mEq. per liter in the level of plasma potassium. Since the pH values in infants frequently fall 0.3 units below normal during severe diarrhea, resultant increments in the levels of plasma potassium may be as great as 3 mEq. per liter. In addition to the effects of low blood pH, the influence of dehydration itself must also be considered as a factor which plays a role in the production of elevated levels of potassium.

On the basis of our observations of the Butler-Talbot method, it appears that modification should be made in order to provide a hydrating solution capable of partially correcting severe acidemia while simultaneously increasing the circulatory volume and improving renal function. Various hydrating solutions for use with the Butler-Talbot

regimen are currently under study, and their usefulness will be described later. By modification of the hydrating solution to achieve earlier partial relief of acidemia, a small increase in sodium dosage is accomplished. This appears to be desirable in light of the hyponatremia which is frequently associated with diarrhea. According to the observations of Darrow and co-workers[27] and Wallace and Moll,[28] the quantity of potassium provided by the Butler-Talbot regimen may be greater than that likely to be utilized by infants. Certainly, adequate renal function is an important prerequisite to the provision of such liberal quantities of potassium. When this regimen is used in infants who are less than 1 month of age, a solution containing less potassium and other electrolytes has been recommended.[29]

During the early phase of treatment by Darrow's method, the plasma bicarbonate and blood pH did not rise so promptly as they were observed to do in the group treated by the modified Hartmann method, but were elevated more promptly than in the group treated by the Butler-Talbot method. After the initial phase of treatment, however, both the level of blood pH and that of plasma bicarbonate showed a steady trend toward the normal range. The overshooting of the normal range was not observed in patients treated by this method. Likewise, low levels of sodium were elevated to the normal range without a tendency toward the development of hypernatremia. In patients with elevated pretreatment levels of plasma sodium, hypernatremia tended to persist during treatment, as observed in the other groups. Normal levels of plasma potassium were promptly attained and/or were maintained without a tendency toward hyperkalemia in patients treated by the Darrow method. In fact, Darrow's method of therapy appeared to be quite satisfactory from every standpoint, except for the initial hydrating solution. The substitution of an alkalinizing solution for the dilute saline solution, as mentioned in one of Darrow's early papers,[30] is the only modification of this method which is suggested by our studies. We feel that M/12 sodium r-lactate with 5 per cent dextrose would be useful for this purpose in the treatment of severe diarrhea of infancy.

The success of any regimen of parenteral fluid therapy is contingent upon the competency of the body's homeostatic mechanisms. Among these mechanisms, the role of the kidneys in regulating composition, tonicity, and volume of body fluids is invaluable.[31, 32] Despite the demonstration of rapid development of concentrating ability,[33, 34, 35] other important renal functions during the early months of life deviate markedly from adult patterns.[36, 37] These deviations of renal function, along with disturbances of other homeostatic mechanisms, must be recognized in the planning of an effective regimen of parenteral fluid therapy for young infants with severe water and electrolyte imbalances.

Rational fluid therapy depends upon accurate diagnosis based upon careful consideration of the medical history, physical examination, and laboratory findings. All of these clinical findings must then be integrated with empirical knowledge concerning requirements and limits of tolerance for correcting specific disturbances of water, electrolytes, calories, and proteins. The changes in body water and electrolytes which occur in infants with diarrhea have been recently summarized by Darrow and Hellerstein.[38] Balance studies have indicated that an average of 9.5 mM. of sodium and 10.4 mM. of potassium per kilogram of body weight are retained during recovery from severe diarrhea.[27] Sodium and chloride are lost from the body in equivalent amounts, but deficits of bicarbonate in the extracellular fluid are accompanied by a decrease in the relative amount of sodium in proportion to chloride.

Changes in the concentration of sodium in the extracellular fluid during acidosis have frequently been attributed to shifts of sodium to the intracellular fluid compartment.[39, 40, 41] Deposition of sodium in bone,[42, 43] as well as changes in extracellular fluid volume and osmolarity,[44] has also been shown to influence the distribution of so-

dium. Animal studies[23, 24] have shown that a high concentration of potassium in muscle is present in metabolic acidosis even in subjects with a deficit of sodium during adequate intake of potassium and chloride. This phenomenon has not been adequately explained. Darrow and Hellerstein[38] state that the loss of proton acceptors accounts for the retention of hydrogen ions in extracellular fluid during metabolic acidosis which accompanies losses of both sodium and potassium. This suggests that in fluid therapy of diarrhea bicarbonate can be repleted only in the presence of adequate quantities of sodium and potassium.

Numerous other therapeutic implications might be drawn from the changes in body water and electrolytes which would further illustrate the complexity of the problems which will confront the practitioner when he attempts to plan an effective regimen of fluid therapy. Therapeutic regimens, incorporating various facets of our knowledge of body fluids and their constituents, have been set forth and modified from time to time. It appears, however, that the gaps in our understanding of the physiology of body fluid, both in health and in disease, have thus far precluded the formulation of a completely ideal regimen of parenteral fluid therapy for severe diarrhea in infants. In view of the availability of several schemes of therapy for severe diarrhea in infants, we feel that comparative studies, such as those presented herein, may prove useful to the practitioner in evaluating their relative efficacy and in modifying them for use in specific clinical situations.

SUMMARY

The efficacy of three methods of parenteral fluid therapy in the repair of abnormalities of fluid and electrolyte balance accompanying severe diarrhea has been evaluated in 53 infants, all less than 15 months of age. Methods studied include a modification of Hartmann's regimen and those of Butler-Talbot and of Darrow. Serial observations before and during treatment with regard to clinical effects, blood pH, and plasma levels of base bicarbonate, sodium, and potassium are compared.

The modified Hartmann method was found to be the most effective of the methods in promptness of relief of severe acidemia and acidosis, but frequently produced alkalemia and alkalosis during the second day of treatment. Deficits of potassium were not adequately repleted and were aggravated in a high percentage of the patients, and levels of plasma sodium frequently rose above the normal range in patients whose pretreatment values were normal or subnormal.

In infants treated by the Butler-Talbot plan, acidemia, acidosis, and hyponatremia persisted over prolonged periods of time. Low levels of plasma potassium rapidly rose to normal, and subnormal pretreatment levels of potassium were often elevated above the normal range. The moderately elevated levels of potassium were unaccompanied by clinical evidence of hyperkalemia.

Levels of blood pH and plasma base bicarbonate in infants treated by the Darrow regimen were slower in returning to the normal range than were those of the patients treated by the modified Hartmann method. Acidemia and acidosis were not so prolonged, however, as in the group treated by the Butler-Talbot regimen. Tendencies to overshoot the normal ranges for blood pH, plasma base bicarbonate, sodium, and potassium were not evident. Low levels of plasma sodium and potassium were effectively repaired by the use of this method.

Hypernatremic infants in all three groups studied (regardless of which treatment method was used) responded to therapy in a similar manner with respect to clinical course and level of plasma electrolytes. All these infants were slow in returning to normalcy.

The advantages and disadvantages of each method of treatment are discussed, and recommendations are made for their modification in accordance with findings of the study.

Dr. J. D. Smith participated in the early studies having to do with the modification of the "Hartmann method" as described. For this we wish to give due recognition.

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Phenylketonuria: some observations on reflex activity

Joseph H. French, M.D.,* David B. Clark, M.D., Harry G. Butler, M.D., and Robert D. Teasdall, M.D.

BALTIMORE, MD.

RECENT interest in patients with phenylketonuria has been directed mainly to early detection and initiation of dietary treatment in an effort to control the elevated blood level of phenylalanine and organic aciduria.[1-4] Although the pathologic lesions have been described as a patchy demyelination throughout the central nervous system,[5-9] the clinical picture is dominated by mental deficiency and convulsions.

In this laboratory interest has been directed to reflexes evoked by peripheral nerve stimulation. These reflexes, while differing in certain respects from naturally produced stretch responses, have the advantage of permitting a reasonable degree of quantitation. In normal adults with threshold stimulation of the tibial nerve, H reflexes (Fig. 1) are recorded from calf muscles. Stronger stimuli also excite motor fibers with a resultant M deflection in the evoked electromyogram which is not reflex in origin. Still stronger shocks are required for F reflexes from the anterolateral muscles.[10] A similar pattern is obtained in patients with an acquired hemiparesis.[11] Only in two situations previously studied are reflex thresholds lowered and H reflexes regularly recorded from the anterolateral muscles. This has been observed by Thomas[12] early in development, and in adult patients with lesions situated in lower brain stem or spinal cord.[11] It seemed possible in phenylketonuria that a failure in the development of the central nervous system or subtle damage to motor tracts in the spinal cord might be present and yet escape detection by means other than those employed in these electrophysiologic reflex studies.

METHODS

Twelve patients with phenylketonuria were investigated for the presence of H reflexes in calf and anterolateral muscles of the leg.[10] The tibial nerve and the peroneal nerve in the popliteal fossa were stimulated electrically with single shocks of varying intensity by means of a needle inserted

From the Division of Neurological Medicine, The Johns Hopkins University School of Medicine and Hospital.

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**Address, Department of Neurology, The Johns Hopkins Hospital, Baltimore 5, Md.*

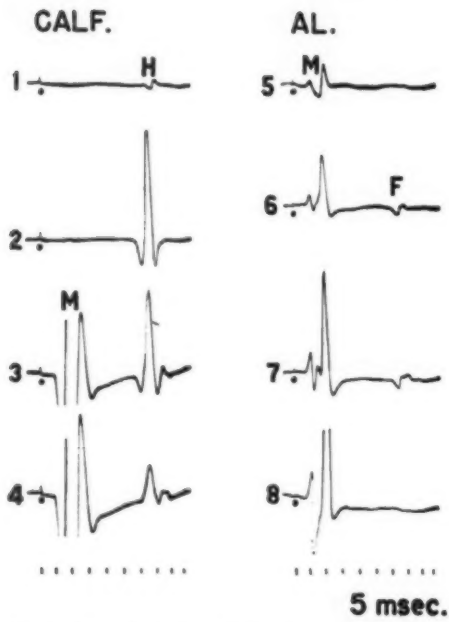

Fig. 1. Normal control. Tracings 1 to 4, action potentials from calf muscle. Single shocks of increasing intensity to tibial nerve. Tracings 5 to 8, action potentials from anterolateral muscles. Single shocks of increasing intensity to peroneal nerve. Stimulus artifact in this and subsequent figures indicated by the small dot.

through skin in close proximity to the respective nerves. The resultant action potentials were recorded through electrodes fixed to skin overlying the calf and muscles in the anterolateral compartments of the leg (anterolateral muscles). These potentials, after adequate amplification, were displayed on a two-beam cathode-ray oscilloscope and photographed.

In addition, 3 groups of subjects served as controls and were investigated in a similar fashion. One group consisted of 10 individuals who were mentally normal and neurologically intact. Another comprised 11 subjects who were severely retarded mentally but neurologically intact. The third group was composed of 10 patients with a congenital or infantile hemiparesis of many years' duration.

Since the observations on these control subjects were based primarily on electrically induced reflex activity, an intact peripheral nervous system was essential. This was ascertained in all subjects by the presence of deep tendon reflexes, H reflexes from calf, and the absence of lower motor neuron involvement or sensory deficit suggestive of a peripheral lesion. This was the only method utilized for the selection of patients comprising the various groups.

RESULTS

Controls.

Normal (intact neurologically and mentally). These 10 patients ranged in age from 7 to 16 years (average age, 10.2 years).

In all individuals, H reflexes were recorded from the calf muscles on stimulation of the tibial nerve. Examples are shown in tracings 1 to 4 of Fig. 1. With threshold stimulation in tracing 1, a potential labeled H was recorded with a latency of 32 milliseconds. The stimulus intensity was increased in tracing 2, and the H reflex became larger. With stronger stimuli employed in tracings 3 and 4, an additional potential, M, appeared. The amplitude of H declined with the stronger stimuli because of blockage by antidromic impulses in motor axons.

On stimulation of the peroneal nerve, an entirely different response was recorded from the anterolateral muscles. This is shown in tracings 5 to 8 of Fig. 1. With threshold stimulation of the peroneal nerve in tracing 5, a response labeled M was recorded. Only with considerably stronger shocks, supramaximal for motor fibers, did reflex responses labeled F appear after a latency of 30 milliseconds. These F reflexes, however, were variable[10] and following some stimuli (tracing 8) the response was absent. In other individuals they were never recorded.

Mentally retarded (neurologically intact). Eleven subjects were included in this group with ages ranging from 6 to 16 years (average age, 12.6 years).

Their I.Q.'s ranged from 45 to 70. They were not sedated prior to the electrical stimulation. The reflex pattern was similar

to the pattern of the preceding group. Low threshold H reflexes were recorded only from calf muscles. Either direct motor responses alone or F reflexes having a higher threshold than motor fibers were recorded from the anterolateral muscles.

Hemiplegia. Eight congenitally hemiplegic patients, and 2 with an infantile hemiparesis, were studied. Their ages ranged from 4 to 22 years (average, 11.5 years). All were ambulatory, exhibited growth arrest, spasticity, weakness, and brisker deep tendon reflexes on the involved side. One patient had a flexor plantar response; the remainder were extensor. All were retarded mentally and 8 of these were subject to convulsions. These patients were not sedated prior to the test. Some were extremely uncooperative and to such a degree that only the hemiplegic limb was studied.

In all patients comprising this group, low threshold H reflexes were recorded from calf muscles on the hemiplegic side. In 4 patients the intact leg was also studied and no differences in threshold or amplitude of the reflex response from calf between the 2 sides were noted.

On stimulation of the peroneal nerve on the hemiplegic side low threshold responses similar to the H reflexes from calf were recorded from anterolateral muscles in 3 subjects. One of these had a bilateral hemiparesis and this reflex pattern was present in both anterolateral groups. In 1 of the remaining 2 patients an F reflex response was recorded from the intact limb, while in the other this extremity was not studied. In the remaining 7 patients, the response from the anterolateral muscles on the hemiplegic side consisted of either direct motor responses alone or high threshold F reflexes.

Phenylketonuria. The 12 patients with phenylketonuria ranged in age from 9 to 26 years (average age, 15.1 years). These patients required institutional care, and were retarded mentally. All subjects had seizures. Five were bedridden and incontinent. The plantar responses were flexor, except in 1 patient who had a unilateral extensor response. The superficial abdominal reflexes could usually be elicited. Voluntary power and muscle tone were essentially within normal limits. The deep tendon reflexes were active, and generally brisker in the lower limbs. In those patients who were bedridden the ankle jerks were not as active and the musculature of the lower limbs was not as well developed as in the ambulatory patients. Two patients had unilateral wasting confined to the leg muscles, accompanied by a depression of the ankle jerk, and absence of H reflex from the calf muscles. These extremities, with presumed peripheral nerve damage, were excluded from the study.

Because of the uncooperative nature of the patients, it was necessary to administer sedation prior to the recording of the elec-

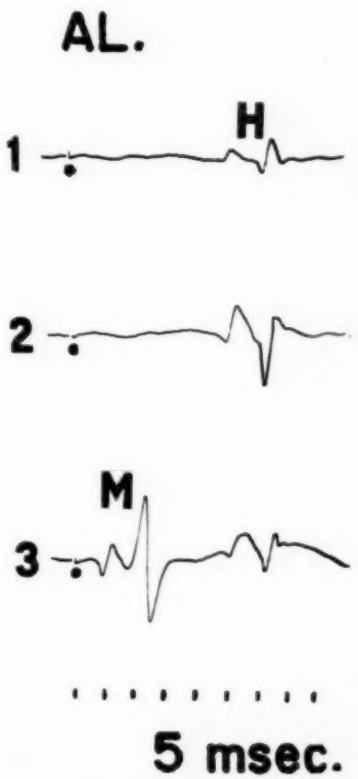

Fig. 2. Phenylketonuria. Action potentials from anterolateral muscles. Single shocks of increasing intensity to peroneal nerve.

trically induced reflexes; this consisted of sodium pentobarbital and morphine sulfate in appropriate quantities. With the levels of sedation employed, there were no changes in the deep tendon reflexes or in the plantar responses.

H reflexes were recorded in all patients from the calf muscles. In 5 patients, stimulation of the peroneal nerve produced low threshold H reflexes in the anterolateral muscles. These findings are shown in Fig. 2. In tracing 1 with threshold stimulation of the peroneal nerve a response, labeled H, with a latency of 25 milliseconds was recorded. The amplitude of the H response increased in tracing 2 with a stronger shock. In tracing 3, the stimulus intensity was further increased and motor fibers were stimulated in addition, as indicated by the initial deflection labeled M.

It is noted, that although low threshold reflexes were recorded from the anterolateral muscles, the amplitude of this H reflex was never as great as that recorded from calf. This is demonstrated in Fig. 3. In tracing 1, the maximal amplitude of the H reflex from calf is shown and is to be compared to the maximal amplitude of the anterolateral H reflex in tracing 2.

All 5 patients who had anterolateral H reflexes were ambulatory. In the remaining 7 patients (5 of whom were bedridden), threshold stimulation of the peroneal nerve produced a motor response and only with considerably stronger shocks were F reflexes recorded. This pattern is similar to that obtained in normal persons (tracings 5 to 8 of Fig. 1).

Fig. 3. Phenylketonuria. Tracing 1, Maximal amplitude of calf H. Tracing 2, Maximal amplitude of anterolateral H.

Table I

	No. of patients	*H reflexes*	
		Antero-lateral	*Calf*
Phenylketonuria	12	5	12
Controls:			
"Normal"	10	0	10
Mentally retarded	11	0	11
Hemiparesis	10	3	10

Three of the patients with anterolateral H reflexes were maintained on a phenylalanine-deficient diet for 3 months. In only 1 of these was a normal blood level of phenylalanine achieved. The electrical studies were repeated in these patients and the results were similar to those obtained prior to the diet.

In Table I the incidence of low threshold H reflexes from anterolateral and calf muscles is depicted for the control and phenylketonuric subjects.

COMMENT

In the control children, the normal group, and those who were mentally retarded but intact neurologically, H reflexes were recorded only from calf muscles while higher threshold F reflexes appeared in the anterolateral muscles. This pattern, shown in Fig. 1, is similar to that previously reported in normal adults.[10]

In patients with a hemiparesis acquired in adult life, damage to descending motor pathways is not sufficient to alter these spinal reflexes from normal.[11] A different response, however, was obtained from the anterolateral muscles in 3 of the 10 children with a congenital or infantile hemiparesis. This consisted of low threshold reflexes with features similar to the calf H reflex. In the remaining patients of this group, the response from the anterolateral muscles was

similar to the other control groups. These patients did not differ in clinical features from the adults with an acquired hemiparesis except for mental deficiency, which alone does not release low threshold H reflexes from anterolateral muscles. The difference in reflex patterns may be attributed to the stage of neurological development at the time of cerebral damage. If the lesion occurs prior to maturation of intraspinal reflex arcs[13] low threshold responses may be released. This state might be related to the observations of Thomas[12] and of Thomas and Lambert[14] in which low threshold reflexes were recorded from the anterolateral and hypothenar groups of muscles in newborn infants. Under these circumstances myelination at cerebral and spinal levels is certainly far from complete. The current observations, then, may suggest that if cerebral damage is acquired in early life, an infantile distribution of the reflex response may be obtained in some patients.

With this in mind, it is interesting to consider the patients with phenylketonuria. In this condition, the pathologic process, presumably metabolic, has occurred prior to maturation at spinal level. Five of the 12 patients had anterolateral H reflexes and this also may be indicative of retention of the infantile reflex pattern. These 5 subjects were ambulatory. The failure to record a similar response in 5 other patients who were bedridden may have been due to peroneal pressure palsies. This would be mainly limited to afferent fibers since motor responses were recorded from anterolateral muscles.

Poser and van Bogaert[9] have described demyelination in the medulla of phenylketonuric patients. It is known that lesions situated at this level release low threshold H reflexes from anterolateral muscles.[11] There was no clinical evidence, however, in the patients with phenylketonuria or children with a hemiparesis, of brain stem or spinal cord damage. Consequently, it seems reasonable to assume that in both groups of patients the presence of anterolateral H reflexes was due to immature spinal reflex arcs secondary to failure of development in descending pathways. It is becoming increasingly evident that not only maturation,[12, 14, 15] but also the impact of disease upon a developing nervous system may be important factors in determining spinal reflex patterns.

SUMMARY

Low threshold H reflexes were recorded from the anterolateral muscles in 5 of 12 patients with phenylketonuria. A similar incidence was noted in patients with a congenital or infantile hemiparesis. It is felt that the enhancement of this reflex activity is related to damage of developing pathways within the central nervous system.

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Hypoglycemia and convulsions in children following alcohol ingestion

Leo H. Cummins, Captain, MC, USA*

INGESTION of alcohol-containing substances is not considered an important cause of poisoning in childhood. In one series of 1,033 cases[1] there were only 6 cases of ingestion of paint solvent, and 2 cases of "alcoholic beverage" intoxication. Hammack,[2] in 1957, reported hypoglycemia in Solox† intoxication; 2 of his patients were children. Euclid Peluffo,[3] in 1958, reported 2 cases of hypoglycemia in children following ingestion of alcohol, but this relationship is not mentioned in the American pediatric literature. Convulsions caused by hypoglycemia as a result of ingestion of medicine, specifically poisoning, are not described in textbooks. Discussing the subject of poisoning, Allway[4] mentions convulsions as being occasionally caused by hypocalcemia, but not by hypoglycemia.

The purpose here is to report 2 cases of alcohol ingestion, each of which was associated with hypoglycemia and convulsions. In the first case the child ingested an unknown quantity of gin, developed severe convulsions, and died. The second child ingested cologne, developed hypoglycemia and convulsions, and improved dramatically after the intravenous administration of glucose solution.

*Address, Pediatrics Section, 97th General Hospital, APO 757, U. S. Forces, New York, N. Y.

†The composition of Solox is: ethyl alcohol 100 parts, methyl alcohol 5 parts, gasoline 1 part, ethyl acetate 1 part, methyl isobutyl ketone 1 part.

CASE REPORTS

Case 1. The first patient was a 6-year-old Negro boy admitted to the 97th General Hospital after ingestion of an unknown quantity of gin.

The patient was apparently well until 7 o'clock on the evening of March 28, 1959, when he drank the gin. He was then put to bed, and the parents went visiting. The parents returned at 2 A.M., and found the boy lying on the floor in convulsions. He reached the hospital at 4 A.M. in a state of constant convulsions. Inquiry into the past history revealed a normal neonatal course and adequate subsequent development. There was no history of accidents or of recent illness. The child had received no injections or medications for several months preceding admission. His appetite had always been good. The past history and family history were negative for convulsions and allergy.

Physical examination at the time of admission revealed a well-developed, slender, 6-year-old Negro male, weighing 45 pounds. He was completely unresponsive and in a state of constant clonic convulsions. The blood pressure was 115/70, and the pulse was 140. Respirations were of the Cheyne-Stokes type. Pupils were pinpoint without reaction to light. A small bump was noted on the forehead but, according to the mother, this had been present before. The remainder of

the physical examination, including funduscopic examination, was unrevealing. Gastric lavage was not done.

Urinalysis showed no sugar or albumin. There were 2 to 3 red blood cells per high-power field and occasional epithelial cells in the microscopic sediment. The initial blood alcohol level at 6:30 A.M. on March 29, 1959, was 20 mg. per cent. At that time the carbon dioxide combining power was 20.5 mEq. per liter and the chloride level was 83.9 mEq. per liter. Blood glucose was 15 mg. per cent, by the Folin-Wu method; spinal fluid glucose was 10 mg. per cent. There was one lymphocyte in the fluid, and culture was negative. After the intravenous administration of glucose, blood sugar determinations ranged from 100 to 200 mg. per cent. A roentgenogram of the skull taken on admission revealed no fracture.

The patient continued to be comatose with convulsions at frequent intervals for the first hours of hospitalization. During the first 30 minutes in the emergency room, 350 mg. of Amytal was administered intravenously. The severity of the seizures was reduced. An intravenous infusion of 5 per cent glucose and water was started at 8 A.M., at least 6 hours after the start of the convulsions. A few minutes later 50 c.c. of 50 per cent glucose was given intravenously, and the convulsions improved markedly. Infrequent focal seizures continued, involving mainly the right arm and face. Amytal, administered intravenously, which had previously been only partially effective, now controlled the seizures. The temperature, blood pressure, pulse, and respirations remained normal. The child continued to be deeply comatose.

At 2:30 P.M., the patient suddenly stopped breathing, and the heart tones became faint. Artificial respiration was given by endotracheal tube. Coramine was given intravenously with no effect. The blood pressure was stabilized at 110 mm. systolic by intravenously administered Aramine. No spontaneous respirations were noted thereafter, and at 6 P.M. the child was placed in a respirator. At 1 A.M., March 30, 1959, the blood pressure dropped to 40 mm. systolic. His color was noted to be good, but the pupils were for the first time completely dilated and fixed. Increasing amounts of Aramine were administered, but the child died at 7 A.M. on March 30, 1959, 27 hours after admission.

Case 2. The second patient, a 3-year-old Negro female, was found comatose at 6 o'clock on the morning of Dec. 19, 1959. She had been entirely well when put to bed the evening before. The parents assumed that she had ingested cologne because of the odor on her breath and of the presence of the nearby bottle. The amount ingested was estimated to be no more than 20 c.c. This was probably ingested in the early morning hours by the patient, who often wandered around at night. Lavage was performed at the local Army dispensary, and she was then sent to the 97th General Hospital for admission.

The child was born at term by a normal delivery. She had no history of severe illness. Development had progressed along normal lines and her appetite was good. There was no history of allergy. No immunizations or other injections had been given recently.

Physical examination revealed a semicomatose 3-year-old Negro girl who weighed 32 pounds. The blood pressure was 76 systolic, and the pulse was 92. There was an odor of perfume on her breath. The pupils were small, and the reflexes were somewhat depressed; the remainder of the physical examination was within normal limits.

Urinalysis on admission showed no sugar or albumin. Acetone was 4 plus, and the microscopic sediment revealed 2 to 3 white blood cells per high-power field. Initial blood chemistry determinations from samples drawn immediately after the convulsions had started showed the carbon dioxide combining power to be 9.1 mEq. per liter; chlorides were 86.3 mEq. per liter; and calcium was 10.6 mg. per cent. Glucose was noted to be 22.5 mg. per cent by the Folin-Wu method. Several subsequent determinations showed a rise in the carbon dioxide combining power and a blood glucose level which rose to 67 mg. per cent, and then to within normal limits.

At 11 A.M., 4 hours after admission, the child began to have convulsions which were mainly tonic, with intermittent clonic movements. Ten cubic centimeters of 50 per cent glucose and 5 c.c. calcium gluconate were given intravenously. A continuous drip of equal quantities of 10 per cent dextrose and water and M/6 sodium lactate was started. Immediately following the administration of the dextrose, there were no further convulsive movements. Thirty minutes later the child opened her eyes, and became much more alert. No visual difficulties or other problems arose during the hospitalization. The patient was discharged on Dec. 22, 1959, to the care of her parents. A subsequent glucose tolerance test was normal.

DISCUSSION

In the cases presented, the role of the hypoglycemia in producing the convulsions is reasonably clear-cut.

The child in the first case ingested ethyl alcohol. The blood alcohol level at the time of the convulsions was 20 mg. per cent. This finding would be against a direct toxic effect of the alcohol on the brain.[5] The blood sugar level of 15 mg. per cent could readily produce convulsions. The child was severely hypoglycemic for at least 6 hours, and it is not surprising that irreversible brain damage and death resulted.

The second child ingested cologne, which consists of 85 per cent denatured alcohol, together with aromatic substances. The amount of methyl alcohol in 20 c.c. of cologne is probably small, but was enough to produce acidosis. Methyl alcohol rarely causes seizures by direct toxic action. The blood sugar level of 22.5 mg. per cent, together with the dramatic response to intravenous glucose, suggests that the convulsions were due to hypoglycemia.

There is great variability in the effects of alcohol on carbohydrate metabolism. In animals, alcohol regularly produces hypoglycemia when the liver has been depleted of glycogen.[6] This observation correlates with the decreased glycogen content of livers of adults dying of acute and chronic alcoholic intoxication with hypoglycemia.[7] In Case 1 the glycogen stores were found to be normal as estimated by microscopic examination of liver sections fixed in absolute alcohol and stained with periodic acid–Schiff reagent. The child died, however, almost 24 hours after the institution of glucose therapy.

Matunaga,[6] experimenting on glycogen-depleted rabbits, found 3 interrelated effects of large doses of alcohol. Initially there was a hypoglycemic effect, then glycogen was formed from the alcohol, and finally there was mobilization of the newly formed glycogen. The hypoglycemic effect was thought to be due to functional hyperinsulinism, but this has been questioned.[8]

The metabolism of alcohol is said to utilize glucose.[10] Acting as a metabolic poison, alcohol could interfere with gluconeogenesis, or inhibit glycogenolysis. These latter hypotheses could explain why the hypoglycemia usually occurs several hours after ingestion of alcohol.[9] Obviously, more data are needed.

SUMMARY

Two instances of hypoglycemia following ingestion of alcohol have been reported. Both children had convulsions, and one of them died. Possible etiological mechanisms are briefly reviewed.

When a child becomes comatose or convulses after ingesting an alcohol-containing substance, hypoglycemia may be present. Blood should be drawn for glucose determination, and 50 per cent glucose should be injected through the same needle.

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"Solubilized" vitamin K_1 (phytonadione) in neonatal hypoprothrombinemia

Milton Shoshkes, M.D.,* Milton Willner, M.D.,

Giacomo Pontoriero, M.D., and Rosita Chiong, M.D.

NEWARK, N. J.

IN 1955, Allison[1] reported the occurrence of kernicterus and hemolytic anemia in premature infants whose only therapy had been relatively high doses of a water-soluble vitamin analogue. This finding has been well substantiated by others,[2-6] and for this reason there has been an active search for a safer type of vitamin K prophylaxis for neonatal hypoprothrombinemia due to the deficiency of this vitamin. The oil-soluble form of vitamin K_1 (phytonadione) has been investigated for this purpose and found to be potent and safe when given parenterally in doses ranging from 1 to 10 mg. intramuscularly[7, 8] and 25 mg. intravenously[9] in the full-term infant, and in doses of up to 10 mg. intramuscularly in the premature infant.[10] No significant hemolytic effect was observed by these authors. This oil-soluble vitamin also has been given orally to the full-term infant in doses of 2 mg.[11, 12] and to premature infants in doses of 10 mg.,[13] with an effective response of the infant's prothrombin times without adverse reactions being noted. This laboratory[12] has found that 2 mg. of phytonadione emulsion administered orally on the first day of life was as effective as the water-soluble menadiol sodium biphosphate given intramuscularly in doses of 2.5 mg. in preventing abnormal elevations of the prothrombin time during the first 5 neonatal days.

More recently, a microsuspension of vitamin K_1 has been made available for clinical testing. Although physically the oil-soluble vitamin remains in a colloidal dispersion, it is a crystalline-appearing, amber-tinted fluid without visible particles, containing 2 mg. of this "solubilized" vitamin per cubic centimeter of isotonic solution, with benzyl alcohol as a preservative.* This material has an advantage over the emulsion, in that it does not "break" with freezing or boiling or after mixing with certain salt solutions, as does the emulsion. Moreover, experience in this laboratory with this "solubilized" vitamin K_1 in adults demonstrated it to be effective after

From the Departments of Medicine and Pediatrics, Newark Beth Israel Hospital.

Assisted by a grant from Merck Sharp & Dohme to the Research Foundation of Newark Beth Israel Hospital.

**Address, 505 Elizabeth Avenue, Newark 12, N. J.*

*Aqua-Mephyton, Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia 1, Pa.

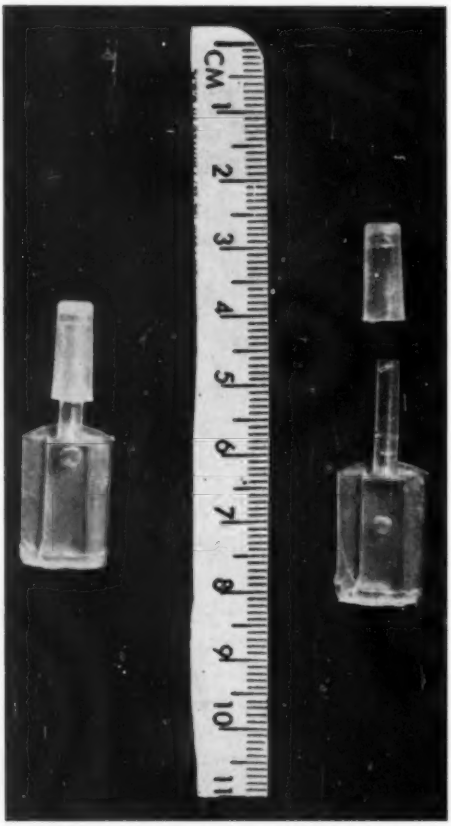

Fig. 1. Photograph of the sterile, disposable plastic oral ampule for "solubilized" vitamin K_1 administration.

intramuscular administration,[14] another advantage over the emulsified vitamin K_1.[15]

Stimulated by these facts, we undertook an investigation of the effectiveness of this "solubilized" vitamin K_1 in preventing neonatal hypoprothrombinemia.

METHOD

At our request, a specifically designed plastic, disposable, sterilized oral ampule was fashioned which contained an amount of the solubilized vitamin adequate to express 2 mg. of the vitamin into an infant's mouth (Fig. 1). Two milligrams of this "solubilized" vitamin K_1 were given orally on the first day of life to all full-term infants born on our ward and semiprivate services. Capillary whole blood specimens were drawn into test tubes 24 to 72 hours later and the prothrombin times were determined by the method previously described.[16] After the initial 44 successful determinations, alternate infants were given 1 mg. of this material intramuscularly on the first day of life, with the prothrombin times determined in similar fashion. After 300 infants were studied in this manner, another group of 52 control infants (not given vitamin K in any form) were studied with similar determinations of the prothrombin times. Two-thirds of all of the prothrombin times in all three groups studied were obtained within the first 48 hours of life.

Indirect and total serum bilirubin values were determined consecutively as well in 60 control infants, in 61 given the vitamin orally, and in 87 given the vitamin intramuscularly. A micromodification of the previously described technique of Malloy and Evelyn[17] was used.

RESULTS

Prothrombin time values were obtained successfully in 52 control infants, in 178 infants given the vitamin K_1 orally, and in 122 infants given the vitamin intramuscularly. These results are summarized in Table I. The mean prothrombin time for the controls was 20 seconds, for the oral group 19 seconds, and for the intramuscular group 17 seconds. As can be seen from the values of the standard deviation from the mean, there

Table I. Mean capillary whole blood prothrombin time values in newborn infants up to 72 hours of life

	No. infants	*Prothrombin time in seconds*	
		Mean	*S.D. from mean*
Control	52	20	6
Oral vitamin K_1 (2 mg.)	178	19	2
Intramuscular vitamin K_1 (1 mg.)	122	17	3

was no significant difference between these mean values upon comparison of any of the groups with one another. The prothrombin times obtained after two routes of administration of vitamin K_1 are further compared in the bar graph, Fig. 2. The distributions of the prothrombin time values are essentially similar in that their ranges are between 10 to 25 seconds, and in that their greatest frequency of distribution lies between 15 and 20 seconds. No abnormal bleeding was noted in any of the treated group of 300 infants. In the control group of 52 infants, however, 2 were found with prothrombin time values greater than our previously observed upper limit of normal of 25 seconds[12]: one was 30 seconds and was associated with extremely free bleeding after skin punctures; in the other infant, whose prothrombin time was indeterminate at first (over 60 seconds), the skin punctures oozed continually for over one hour despite pressure dressings. Each of these infants received 2 mg. of vitamin K_1 orally and each had normal prothrombin time levels, within 24 hours. A circumcision was performed on the second infant 2 days after vitamin K_1 was given without any unusual bleeding being observed.

Table II summarizes the serum bilirubin values obtained in this study. The control group had a mean indirect bilirubin of 0.6 mg. per cent, and a total of 1.8 mg. per cent. The oral administration group had a mean indirect bilirubin level of 0.7 mg. per cent, and a total of 1.9 mg. per cent. The infants who received the intramuscular preparation had a mean indirect bilirubin value of 0.4 mg. per cent, with a total of 1.4 mg. per cent. There were no significant differences between any of these groups. The maximum elevation of indirect bilirubin was 1.8 mg. per cent in each of the groups; the total levels were also quite similar, ranging from 5.0 mg. per cent in the control group to 7.5 mg. per cent after the oral dose.

DISCUSSION

This study demonstrates the feasibility of administering the "solubilized" form of vitamin K_1 orally to newborn infants within the first few hours of life. There is no advantage in its parenteral administration except

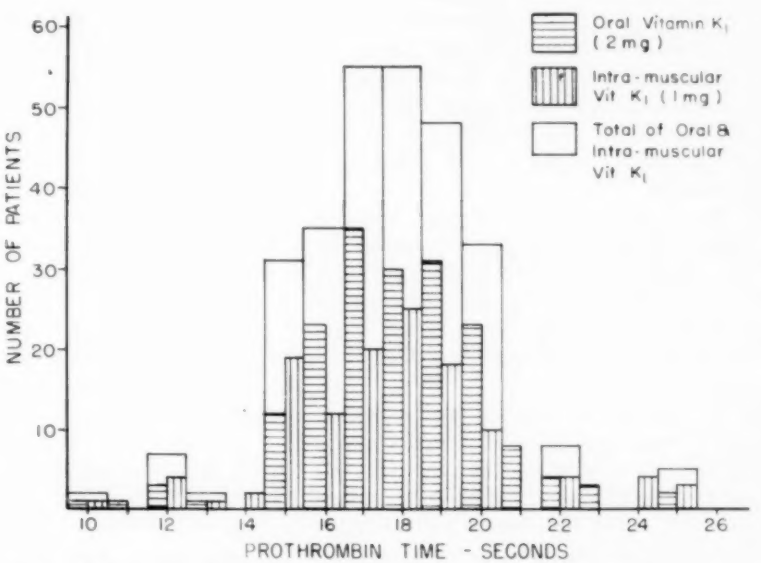

Fig. 2. The distribution of capillary whole blood prothrombin times (capillary test-tube method) after oral and intramuscular administration of "solubilized" vitamin K_1.

Table II. The mean and maximum values for indirect and total serum bilirubin levels in newborn infants up to 72 hours of life

		Mean bilirubin levels		*Maximum bilirubin levels*	
	No. infants	*Indirect (mg. %)*	*Total (mg. %)*	*Indirect (mg. %)*	*Total (mg. %)*
Control	60	0.6	1.8	1.8	5.0
Oral Vitamin K_1 (2 mg.)	61	0.7	1.9	1.8	7.5
Intramuscular (1 mg.)	87	0.4	1.4	1.8	6.0

in the infrequent instances where an oral feeding is impossible. No infant given this material orally failed to attain a normal prothrombin time and none had any evidence of a bleeding diathesis. No untoward reactions were observed and the bilirubin determinations were well within normal neonatal limits.[18, 19] There is of course the possibility that further experience with this material may uncover untoward reactions but, in our experience, it has been a safe material. The use of this vitamin orally was facilitated greatly by the introduction of the oral ampule; the Nursery nursing staff found that the premeasured dose in the sterilized and disposable ampule was a great convenience, and moreover, the infants sucked the vitamin avidly from the nipple-like tip without signs of distaste.

The justification for the continuation of vitamin K prophylaxis for hemorrhagic disease of the newborn has been substantiated in this country by Vietti and collaborators,[20] in Cuba by Aballi and his co-workers,[21] and for South African Negroes and Indians by Shepherd.[22]

Our past experience,[12] as well as that recorded here, confirms the potential danger of an elevated prothrombin time when administration of vitamin K has been omitted. Since the safety and therapeutic efficacy of vitamin K_1 in an oral dose of 2 mg. now seems well established, there appears to be little argument against its use for the general prophylaxis of neonatal hypoprothrombinemia.

An extensive application of this prophylactic measure presents itself. Since neonatal hypoprothrombinemia responds well and for a prolonged time to the single oral dose of vtiamin K_1, there is a potential for eradication of an illness by the administration of this drug by medically unskilled personnel. Infants born in the underdeveloped areas of Asia, Africa, and South America are usually delivered at their homes by midwives. These relatively unskilled personnel are not competent to give injections to the newborn; moreover, superstition and taboo probably would forbid the use of such injections. Midwives could, however, be readily trained in the use of the described oral ampule. These sterilized ampules remain stable without particularly stringent environmental precautions and could be used in many of the underprivileged areas.

SUMMARY

Solubilized vitamin K_1 (phytonadione) was administered to a group of 300 infants during the first day of life. One hundred and seventy-eight received 2 mg. orally via a specially designed disposable, sterilized plastic ampule, and 122 received 1 mg. intramuscularly. Capillary whole blood prothrombin times in all of the infants and serum bilirubin levels, indirect and total values, in a portion of them were determined within the subsequent 72 hours of life and compared to those of a control group. There were no significant differences between the prothrombin times or the bilirubin levels of the several groups. Two of the 52 control infants, however, had prolonged prothrombin times.

The prothrombin times of all infants in the vitamin K_1-treated groups were within normal limits, and no bleeding tendencies were noted. No untoward reaction to either method of administration of vitamin K_1 was encountered.

We wish to thank Miss Mollie Hanson, R.N., Nursery Supervisor, and Miss Rae Katz, Assistant Nursery Supervisor, for their close co-

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Neonatal thyroid function: erythrocyte T_3 uptake in early infancy

J. Marks, M.D., J. Wolfson, M.D., and R. Klein, M.D.*

PITTSBURGH, PA.

SEVERAL reports have contained evidence suggestive of increased thyroid function in the neonatal period. Elevated protein-bound iodine values were reported by Danowski.[1] These were highest on the third day of life but fell precipitously during the first six weeks of life, and then more slowly until adult levels were reached at the end of the first year. Man[2] found similar changes in the butanol extractable iodine values. In 1954, Van Middelsworth[3] demonstrated that the thyroid uptake of I^{131} in 7 normal 2- to 3-day-old males was significantly above adult levels. Both PBI and I^{131} uptake values, however, may be elevated in certain types of hypothyroidism and in euthyroid individuals with goiters.[4, 5] The introduction by Hamolsky[6] of the measurement of erythrocyte triiodothyronine uptake as an index of thyroid function afforded the opportunity of investigating another parameter of neonatal thyroid function. The present study was designed to evaluate the possibility of increased thyroid-binding globulin in the newborn as a cause for the increase in protein-bound iodine, and to establish that these changes were not solely the result of transplacentally transfused material.

From the Department of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, and Elizabeth Steel Magee Hospital.

Study supported in part by the Health Research and Services Foundation, Grant A-11.

**Address, Department of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh 13, Pa.*

METHODS

Hamolsky's procedure for measuring the in vitro red cell uptake of I^{131}-labeled triiodothyronine was utilized. In this method $36 - 144 \times 10^{-4}$ mcg. of triiodothyronine in 0.1 ml. volume is incubated at 37° C. for 2 hours with 3 ml. of whole blood. The specimens are continuously agitated during this period. Following incubation, two 1 ml. aliquots are counted in an appropriate well-type scintillation counter. The red cells are then washed with 10 ml. volumes of isotonic saline five times, resuspended in 1 ml. saline, and counted. The hematocrit is determined simultaneously for each specimen. After necessary corrections for background are made, the amount of radioactivity in the erythrocyte, corrected to 100 per cent hematocrit, is compared to that of the whole blood and multiplied by 100. This is labeled per cent triiodothyronine or T_3 uptake. Heparinized blood was used throughout our studies. The mean difference between the

two 1 ml. aliquots counted was less than 5 per cent.

In a preliminary experiment, the erythrocyte T_3 uptake was measured in blood obtained from normal adults after separation of the cells and plasma and reconstitution of the blood so as to produce aliquots with roughly 25, 50, and 75 per cent hematocrits. To these was added 72×10^{-4} mcg. of radioactive triiodothyronine. In one experiment measurements were also made with 36 and 144×10^{-4} mcg. of T_3. In another single experiment the red cells were washed with 5 and 15 ml. aliquots of saline as well as with 10 ml. volumes. Subsequently all assays were carried out by the Hamolsky technique, which was modified so that the hematocrit of the blood assayed was reconstituted to a range of 42 to 50 per cent.

The following groups of subjects were utilized: Adult laboratory personnel, hospitalized children 1½ to 15 years of age, full-term and premature infants of various ages, and pregnant women at delivery. The older children were free from obvious endocrine abnormality and from any acute illness. The infants were born of normal deliveries, and were considered healthy upon examination in the lying-in hospital or at the well-baby clinics where the blood was obtained. Blood was obtained at delivery from 7 mothers and from the cords of their infants. Repeat determinations on the same infants were made at 3 to 5 days of age.

In addition to the erythrocyte radioactive T_3 uptake, butanol extractable iodine (BEI)* was also measured in some cases.

RESULTS

A number of blood specimens from adults were adjusted to three different hematocrits and the uptakes compared for the three hematocrits for each specimen. As noted from Table I, the uptakes for the adjusted high hematocrits are higher and those for the adjusted low hematocrits lower than those observed for specimens of the same blood at a normal hematocrit. Fourfold variation in the amount of radioactive T_3 employed, and the threefold changes in the volume of the saline wash did not affect the test results.

Table I. Effect of hematocrit on per cent erythrocyte T_3 uptake. Blood specimens from 4 normal adults reconstituted to three arbitrary hematocrits each

	Hematocrit		
Subjects	*74-76 %*	*46-49 %*	*22-26 %*
I	14.5*	11.4	8.2
II	24.4	18.3	11.1
III	23.8	14.0	10.3
IV	29.0	17.9	13.3

*54 hematocrit.

Table II and Fig. 1 portray results from one experiment where aliquots of a sample of "normal" adult blood were reconstituted to hematocrits of 22, 48, and 76 per cent. The per cent erythrocyte T_3 uptakes for the three levels of hematocrits were 10, 15, and 24 per cent. No significant difference in uptake was produced in the 48 per cent hematocrit specimen by varying the dose of T_3 added from 36 to 72 to 144×10^{-4} mcg. Table III gives the results of a similar experiment in which one dose of radioactive T_3 was used, but the volume of the saline washes was varied from 10 to 15 c.c. for the high hematocrit and to 5 ml. for the low hematocrit. As may be seen, this had no perceptible effect.

A small group of normal adults and a larger group of hospitalized children, aged 1½ to 15 years, were studied. The mean erythrocyte T_3 uptake for 8 normal adults and 40 older children without known disease was 13.4 and 13.9 per cent, respectively. This level does not differ significantly from the normal euthyroid range for adult and juvenile subjects reported by Hamolsky[6, 7] and by Crigler[8] of 10 to 17 per cent with a mean uptake of 13.9 per cent.

Table IV records the per cent T_3 uptake of healthy, full-term infants. The mean value for cord blood, 16.3 per cent uptake, was

*BEI determinations were made by Bio-Science Laboratories, Los Angeles, Calif.

significantly greater than that shown for the older children with a probability of less than 0.01 of this being due to chance. The mean of older, well, full-term infants 3 to 9 days of age was 19.8 per cent, which is again significantly greater than the cord blood value. At 2 to 4 weeks of age, the mean T_3 uptake was significantly less than that at the latter part of the first week ($p < .05$), but it was still higher than that of normal, older children ($p < .01$). The mean level of T_3 uptake for the group of patients 6 to 9 weeks of age was in the normal range for older children and adults and was significantly lower than that of the 2- to 4-week-old newborn infants. Thus, the per cent T_3 uptake reaches a maximum in the first week of life and falls to within normal adult values by 6 to 9 weeks of age. Fig. 2 portrays the mean T_3 uptake for full-term, normal newborn infants at different periods of life as compared to the mean and range for normal older children and adults.

Table II. Effect of hematocrit and dose of triiodothyronine (T_3) on per cent erythrocyte T_3 uptake. Blood from a single adult reconstituted to three arbitrary hematocrits and incubated with variable T_3 dosage.

Dose of T_3 ($\gamma \times 10^{-4}$)	*Hematocrit*		
	76%	*48%*	*22.5%*
144	26.8	15.3	10.1
72	24.5	14.0	10.3
36	23.7	15.0	8.0

Table III. Effect of hematocrit and of volume of isotonic saline wash on per cent erythrocyte T_3 uptake. Blood from a single adult adjusted to three different hematocrits and washed with variable amounts of normal saline

Volume saline wash	*Hematocrit*		
	74%	*47%*	*26%*
15 c.c.	29.3	—	—
10 c.c.	29.0	17.9	13.3
5 c.c.	—	—	13.0

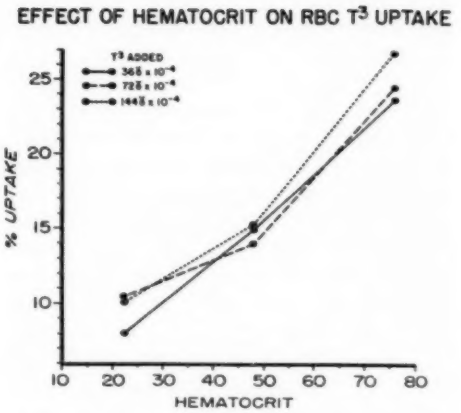

Fig. 1. Per cent erythrocyte T_3 uptake of 9 aliquots of blood reconstituted from a single sample from a normal adult.

Table V and Fig. 3 present the results of similar measurements as well as measurements of butanol extractable iodine in a group of mothers and their infants. Blood was obtained from both the mother and the infant's cord at delivery and again from the infant at 3 to 5 days of age. Cord erythrocyte T_3 uptake was significantly higher than the maternal T_3 uptake, while that for the 3- to 5-day-old infants was still higher. Similar findings were also observed in another group of 11 paired cord and infant specimens. Erythrocyte T_3 uptake for the mothers was 11.3 per cent, which is significantly lower than that of normal adults, corroborating Hamolsky's[6] observations. Parallel determinations of BEI are recorded for 5 of the 7 sets of infants studied in this special group. It will be noted from the values shown in the table that the BEI's for the cord bloods are high but distinctly less than the maternal values, while there is again an increase at 3 to 5 days. Thus, the relationship of the BEI to per cent T_3 uptake in maternal blood differs from that in infant cord blood.

Premature infants were then compared with full-term infants. Eleven healthy prematures 3 to 9 days of age showed a mean uptake of 26.5 per cent, compared to a mean of 19.8 per cent for full-term infants of a

similar age. Nine prematures, 2 to 4 weeks of age, had a mean of 25.0 per cent, as opposed to 17.5 per cent for the full-term infants of the same age. The mean for premature infants 6 to 9 weeks of age, 23.3 per cent, differs from the mean of 13.2 per cent for full-term infants of the same age. The differences between all three pairs are significant; the probability of this being due to chance is less than 0.01. Thus, the level of uptake in premature infants is higher than the level of uptake in full-term infants at the same age (Table VI and Fig. 4). Butanol extractable iodine values in 5 premature newborn infants were not higher than those in full-term infants.

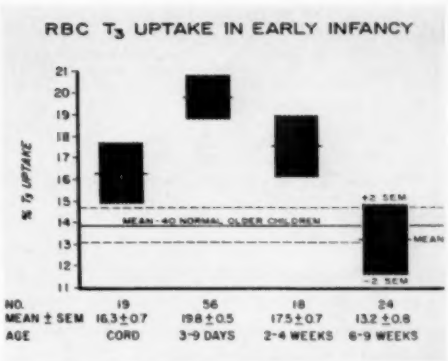

Fig. 2. *S E M* = Standard error of the mean. Dotted lines represent 2 standard errors above and below the mean for 40 "normal" children, 1½ to 15 years of age.

Table IV. Per cent erythrocyte T_3 uptake of full-term infants

Age	*No. of subjects*	*Mean ± standard error*	*Significance*	
			Comparison with preceding age group	*Comparison with "normal" children from 1½ to 15 years*
Cord	19	16.3 ± 0.7	—	$p < 0.01$
3 to 9 days	56	19.8 ± 0.5	$p < 0.01$	$p < 0.01$
2 to 4 weeks	18	17.5 ± 0.7	$p < 0.05$	$p < 0.01$
6 to 9 weeks	24	13.2 ± 0.8	$p < 0.01$	$p > 0.1$

DISCUSSION

Hamolsky[7] has offered the following explanation of the mechanism of the test. Although several plasma protein elements bind thyroid hormone, it is believed that one, an alpha globulin, binds material more firmly than the others. Erythrocyte T_3 uptake is apparently directly related to the degree of saturation of alpha-globulin binding sites by thyroxin-like material. Whether the effect noted is a specific competitive relationship between the red cell and the plasma binding sites, or whether this phenomenon is a result of saturation and overflow is as yet somewhat uncertain. In any event, for practical purposes, it could be postulated that in hyperthyroidism more of the presumed binding sites would be occupied so that the added triiodothyronine would be attached to the more loosely bound sites, and thence to the surface of the red cells producing the elevated erythrocyte T_3 uptake. The converse would occur with hypothyroidism.

Although triiodothyronine uptake on the red cell usually parallels other parameters of thyroid function, there are situations where the protein-bound iodine is elevated and the triiodothyronine uptake is depressed. An example of this is found in pregnancy, where there is a primary increase in thyroid-binding globulin and an elevated circulating PBI secondary to the increased binding capacity. Ingbar[9] has shown that thyroid-binding protein is greatly increased during pregnancy and to a lesser but significant degree in cord plasma. Thus, red blood cell T_3

Table V. Per cent erythrocyte T_3 uptake in a paired series of mothers and their infants

	T_3 Uptake	*Significance*	*BEI (mcg./100 ml.)*	*Significance*
Mother	11.3 ± 0.4	—	8.1 ± 0.4	—
Cord	14.8 ± 0.9	$p < 0.01$	5.6 ± 0.5	$p < 0.01$
Infant	21.3 ± 0.9	$p < 0.01$	9.1 ± 0.7	$p < 0.01$

Table VI. Per cent erythrocyte T_3 uptake of full-term and premature infants

Age	*Full-term infants*	*Premature infants*	*Significance*
3 to 9 days	19.8 ± 0.5 (56)*	26.5 ± 1.2 (11)†	$p < 0.01$
2 to 4 weeks	17.5 ± 0.7 (18)	25 ± 1.6 (9)	$p < 0.01$
6 to 9 weeks	13.2 ± 0.8 (24)	23.3 ± 1.9 (5)	$p < 0.01$

*Number of subjects in parentheses.

†The mean BEI for 5 of these premature newborn infants is 6.5 mcg. per 100 ml. with a S.E.M. of ± 0.3.

uptake probably reflects two factors: (1) the level of circulating thyroid-binding protein, and (2) its relative level of saturation by circulating thyroid hormone.

One could postulate that in a specimen with a low hematocrit the larger plasma volume would contain relatively more thyroid-binding protein and consequently erythrocyte T_3 uptake values would be falsely low. Our results showing an increase in erythrocyte T_3 uptake parallel to an increase in hematocrit afford some evidence that this may be so. Other explanations are possible, however. Among these was one suggested by the work of Meade,[10] who reported that erythrocyte T_3 uptake was inversely proportional to the amount of washing of the red cells. However, we were unable to find any evidence to confirm this possibility in the single experiment carried out with different volumes of saline washes. Because of the wide variation in hematocrit seen in early infancy, all assays in the body of this report were carried out by the modification of Hamolsky's technique with the hematocrit adjusted to within the adult range (from 42 to 50 per cent) at the start of the procedure.

When Danowski[1] first reported on his findings in 1951, he discussed several different possible explanations of the elevated protein-bound iodine noted in the first year of life: (1) that this represented a true increase in thyroid function, and (2) that the findings could be explained by changes in extracellular fluids usually seen in newborn infants. Danowski discarded the latter theory, however, because this would not explain the persistence of elevation throughout as long a period as he demonstrated. In addition, the magnitude of changes in fluid volume are not great enough to explain the elevations of protein-bound iodine.

Danowski also raised the possibility that the infant metabolized thyroid hormones at a slower rate. This seems unlikely, however, in view of the work of Stevenson,[11] who showed that premature infants could ingest 120 to 180 mg. thyroid daily without clinically manifest toxicity. Another explanation for the elevated PBI or BEI, not discussed by Danowski, is in terms of some hormonally inert iodinated protein. At the present time, however, investigation of this possibility is not feasible since it would require the in vivo use of radioisotopes in newborn infants.

Danowski gives two other possibilities: (1) that the elevated PBI is secondary to an increased plasma thyroid-binding capacity, and (2) that it is a reflection of transplacentally transfused material.

It will be noted that there is a difference between the triiodothyronine uptake and the protein-bound iodine in the newborn as com-

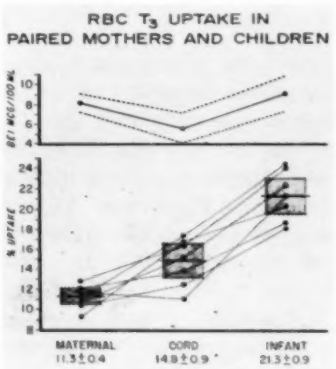

Fig. 3. Mean ± standard error for per cent T_3 uptake shown at bottom of graph.

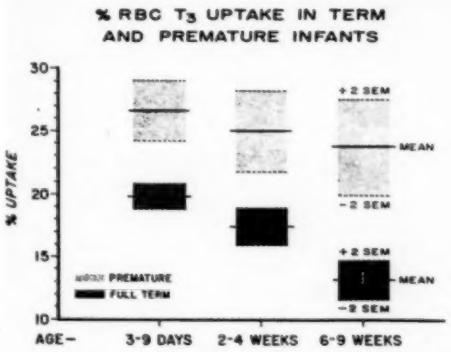

Fig. 4. *S E M* = Standard error of the mean.

pared with that of the mother. In the maternal serum, the PBI or BEI is elevated secondarily to an increased thyroid-binding protein as was previously demonstrated by Ingbar.[9] Both our findings and those of Hamolsky,[6] however, show a depression of the per cent T_3 erythrocyte uptake in maternal blood. In addition, observations show that the cord blood obtained from the infants of the same mothers has a somewhat smaller BEI but an erythrocyte T_3 uptake which is significantly greater both than that of the mothers and that of normal older children or adults. These changes show a significant discrepancy between the normal and umbilical cord findings. Thus, it is strongly suggested that the changes observed are more than a reflection of maternal thyroid status in the infant.

The finding of an elevated erythrocyte T_3 uptake in the newborn makes it seem impossible to explain the concurrently elevated PBI or BEI solely on the basis of an elevated thyroid-binding protein. If the increased PBI were secondary to an increased thyroid-binding capacity, one would expect a low T_3 uptake and a high PBI, as seen in pregnancy.

Our findings, coupled with those of Danowski and of Van Middelsworth, strongly suggest that there is a true increase in thyroid function in the newborn period. The finding of a more elevated T_3 uptake in the premature, who has a BEI within the range of normal for full-term newborn infants, suggests that the thyroid-binding protein is less elevated in the premature than in the full-term infant.

SUMMARY

1. The erythrocyte T_3 uptake method of Hamolsky has been modified so that it is adaptable to individuals in the pediatric age range.

2. Using this technique, we have shown elevated erythrocyte T_3 values in the full-term neonate. These fall to within the adult range when the infant is 6 to 9 weeks of age. The elevation of erythrocyte T_3 uptake appears more marked and more prolonged in the premature infant.

3. The elevated erythrocyte T_3 uptake shows that the increased protein-bound iodine or butanol extractable iodine of the neonate is not the result of an increased thyroid-binding protein. The different relationships of the T_3 uptake to the BEI in the maternal and in the cord blood specimens indicate that the observations in the newborn are not merely a reflection of maternal thyroid status. Our data suggest that there is a true increase in thyroid secretion in the newborn infant.

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A strange cause of death

English newspapers have recently reported the death of a 9-year-old boy caused by inhaling gasoline fumes. For some time the parents had observed the strange attraction of the boy for gasoline fumes and had reprimanded and punished him. On the fatal day, while his father was working nearby, the boy crept under a canvas sheet which covered his father's motorcycle and removed the cap from the gasoline tank. After being missed for three hours he was discovered dead with his face beside the open gasoline tank.

Congenital dextrocardia

Clinical, angiocardiographic, and autopsy studies on 50 patients

Rene A. Arcilla, M.D., and Benjamin M. Gasul, M.D.*

CHICAGO, ILL.

DEXTROCARDIA is a fascinating and an intriguing subject not only to students of physical diagnosis but also to embryologists and cardiophysiologists. While earlier studies on this subject have been reported casually as a matter of academic interest, dextrocardia is assuming greater importance because it is often accompanied by cardiac anomalies that may be amenable to palliative or corrective surgery. Dextrocardia associated with situs inversus is a well-known entity. The cases previously described in the literature as isolated dextrocardia without situs inversus, which we classify as dextroversion complex or mixed dextrocardia, are almost always accompanied by severe congenital malformations of the heart. Dextrocardia due to anomalies of the lungs, diaphragm, or of the chest cage usually has no associated cardiac anomalies. The literature on dextrocardia is replete with many terminologies and classifications[1-9] which reflect the confusion in the concepts regarding the various entities.

This report is based on studies of 50 cases of congenital dextrocardia. The clinical, roentgenologic, and electrocardiographic findings were correlated with the abnormal position and anatomy of the heart as derived from angiocardiographic, hemodynamic, and autopsy data.

MATERIALS AND METHOD

The data on 55 cases of congenital dextrocardia were reviewed; the data on 5 patients were incomplete and were not included in this study. Since this paper deals only with congenital dextrocardia, patients with extrinsic displacement of the heart secondary to acquired diseases of the chest were excluded. There were 26 males and 24 females. The ages varied from birth to 12 years except for an adult aged 55 years. All patients with the exception of 4 newborn infants had roentgenograms of the chest in the conventional posteroanterior, right anterior oblique, and left anterior oblique views. In about a fifth of the cases, complete gastrointestinal roentgenographic examinations were performed. A 15-lead electrocardiogram was taken routinely and in a few patients additional right precordial

From the Pediatric Cardiophysiology Department, Cook County Children's Hospital and Hektoen Institute for Medical Research, Chicago, and the Department of Pediatrics, University of Illinois College of Medicine, Chicago, Ill.

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Address, Pediatric Cardiology, Cook County Children's Hospital, Chicago 12, Ill.

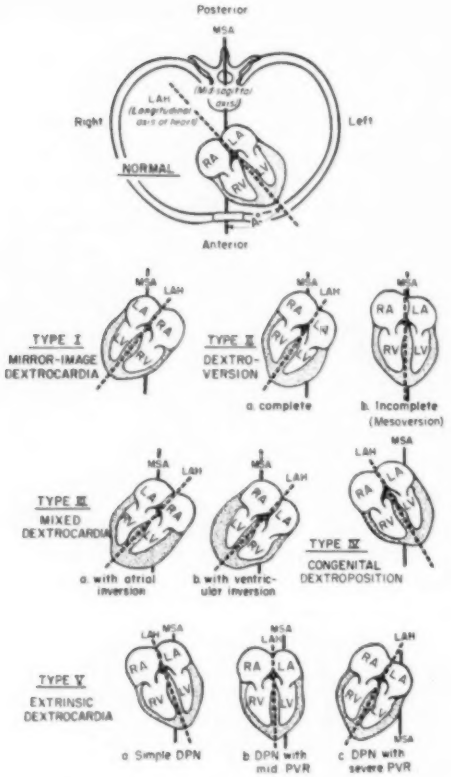
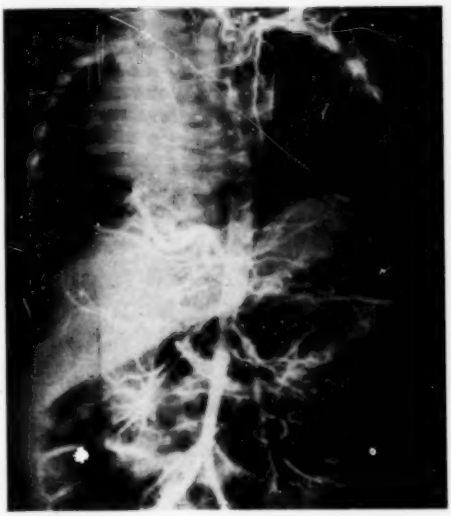


Fig. 1. Classification and diagram of the position of the heart and arrangement of its chambers in the various types of dextrocardia. The angle *(A°)* formed by the longitudinal axis of the heart *(LAH)* with the midsagittal axis of the chest *(MSA)* in the horizontal plane indicates the degree of cardiac heterotaxy. A transverse section of the chest demonstrating the position and chamber arrangement of a normally placed heart is presented for comparison. *DPN* = dextroposition; *PVR* = pivotal rotation.

and scapular tracings were also taken. The mean auricular vectors in the frontal and horizontal planes were determined from these tracings by the method of Zao and co-workers.[10] During the last year vectorcardiograms were obtained utilizing the cube system of Grishman. The vector loops were recorded by the Sanborn vector system and visoscope. Cardiac catheterization was performed in the conventional manner. The pressure measurements were obtained with a Sanborn electromanometer assembly, and blood oxygen was determined by the Van Slyke technique. The relative position of the cardiac chambers was evaluated by noting the location of the catheter during fluoroscopy and by spot roentgenograms taken in the posteroanterior and lateral views. In the first 9 years of this study, the angiocardiograms were performed with a Fairchild roll-film serial changer at a speed of 2 exposures per second in a single plane. In most patients repeat angiocardiograms were taken in another plane. In the last 4 years, the Elema angiocardiographic apparatus has been in use and radiograms are taken simultaneously in 2 planes at a maximum speed of 8 to 12 exposures per second. Angiocardiography was performed on 40 patients, cardiac catheterization on 13, surgery on 9, and 20 patients had postmortem examinations.

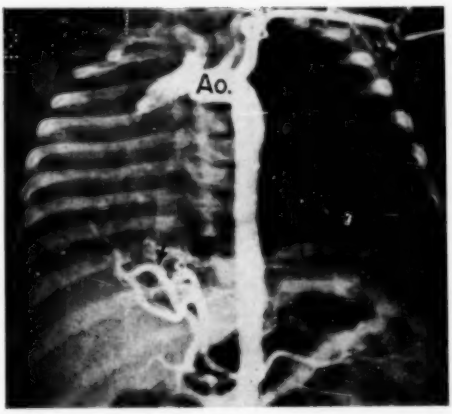
Each case was studied with special attention to the position of the heart, the locations of the cardiac chambers and of the great vessels as derived from the angiocardiograms, and from the findings at surgery and at necropsy. The degree of dextrocardia was determined from the angle formed by the longitudinal axis of the heart with the midsagittal axis of the chest in the horizontal plane (Fig. 1). In a normally located heart, this angle is about 40 degrees to the left of the sagittal axis. We have considered an angle of 30 to 40 degrees to the right of this axis as indicative of "complete" dextrocardia, and an angle from 0 to 20 degrees to the right of this axis as indicative of an "incomplete" type of dextrocardia. This angle therefore reflected the degree of cardiac heterotaxy in the intrinsic group (Types I, II, III, and IV) or the degree of pivotal rotation of the heart along the horizontal plane in the extrinsic group (Type V) of dextrocardia. The term, intrinsic, denotes a dextrocardia due to a developmental anomaly of the embryonic heart per se, independent of diseases or anomalies of its surrounding structures.

We classify dextrocardia in 5 major types



A

C



B

Fig. 2. Retrograde aortography on 3 patients with extrinsic dextrocardia and with aberrant systemic arteries supplying the right lung. In *A* (Case 37) and *B* (Case 50) the arteries arise from the abdominal aorta. In *C* (Case 36) they arise from an anomalous right subclavian artery.

using the position of the heart and the arrangement of the cardiac chambers as points of reference. These are:

Type I, mirror-image dextrocardia
Type II, dextroversion complex
Type III, mixed dextrocardia
Type IV, congenital dextroposition
Type V, congenital extrinsic dextrocardia

The arrangement of the cardiac chambers in the various types as viewed in a horizontal transection of the chest is illustrated in Fig. 1. Following a brief presentation of the extracardiac and intracardiac anomalies in our 50 cases we shall present the angiocardiographic, roentgenologic, and electrocardiographic features of these 5 types.

EXTRACARDIAC AND INTRACARDIAC ANOMALIES

Table I is a summary of the various types of dextrocardia and the associated cardiac and extracardiac anomalies in the 50 cases

Table I. Summary of 50 cases of congenital dextrocardia

Patient	Age*	Dextrocardia		Situs inversus	Intracardiac anomalies‡	Extracardiac anomalies	Special studies	Autopsy
		Type	Degree†					
1 R. B.	9 months	I	C	+	–	–	Angio.	–
2 C. C.	7 months	I	C	+	–	–	Angio. Cath.	–
3 A. W.	4 months	I	C	+	–	–	Angio.	–
4 Ch. C.	11 months	I	C	+	–	–	Angio.	–
5 B. D.	12 years	I	C	+	–	–	Angio. Cath.	–
6 M. M.	3 months	I	C	+	Tricuspid stenosis; VSD; transposition of GV; preductal coarctation	Absent right kidney	–	+
7 T. M.	3 months	I	C	+	Severe tetralogy; ASD	Asplenia; anomalies of celiac and mesenteric vessels	Angio.	+
8 M. B.	2 weeks	I	C	+	Severe tetralogy	–	Angio.	–
9 G. R.	2½ years	I	C	+	Severe tetralogy	–	Angio.	–
10 G. S.	11 months	I	C	+	Single ventricle with PS; ASD; double SVC	–	Angio.	–
11 F. S.	2 months	I	C	+	Common A-V canal	–	Angio.	–
12 B. S.	Stiliborn	II_a	C	–	Pseudotruncus; double SVC	–	–	+
13 T. P.	7 weeks	II_a	C	–	Pseudotruncus; PDA	–	–	+
14 C. D.	5 months	II_a	C	–	Mitral stenosis or atresia; VSD; partial transposition of great vessels; double SVC	–	Angio. Cath.	–
15 R. H.	7 years	II_a	C	–	ASD	–	Angio. Cath.	–
16 M. M.	7 weeks	II_a	C	–	Severe tetralogy; PDA	–	Angio.	–
17 E. R.	6 years	II_a	C	–	Tetralogy	–	Angio. Cath.	–
18 J. M.	3 years	II_a	C	–	ASD; double SVC	–	Angio. Cath.	–

18	J. M.	3 years	II_a	C	–	ASD; double SVC	–	Angio. Cath.	–
19	C. T.	11 months	II_a	C	–	Single ventricle with pulmonary stenosis; ASD; double SVC	–	Angio.	–
20	D. G.	10 months	II_a	C	–	Tetralogy	–	Angio. Operation	–
21	M. W.	4 years	II_a	C	–	VCD; transposition of GV with pulmonary stenosis	–	Angio. Cath.; operation	–
22	W. W.	55 years	II_b	Inc.	–	–	Diverticulosis of small intestines	Angio.	–
23	R. H.	1 week	II_b	Inc.	–	Tricuspid atresia with pulmonary atresia; ASD; VSD	–	Angio.	+
24	J. Mc.	3 years	II_b	Inc.	–	VSD with transposition of GV and pulmonary stenosis	–	Angio. Cath.	–
25	B. P.	1 year	II_b	Inc.	–	Tetralogy; juxtaposed atrial appendages	–	Angio.	+
26	D. R.	9 months	II_b	Inc.	–	Partial pulmonary venous drainage to left innominate vein	Marfan's syndrome	Angio. Cath.	–
27	T. B.	13 months	III_a	Atrial inversion	–	Mitral (right) atresia; ASD; VSD	–	Angio. Cath.	–
28	N. F.	1 week	III_b	Ventricular inversion	–	Atresia of right A-V orifice; pulmonary atresia; ASD; VSD; PDA; double SVC	–	Angio. Operation	+
29	T. G.	2½ months	III_b	Ventricular inversion	+	Pseudotruncus; mitral stenosis; PDA; double SVC	Asplenia; incomplete rotation of cecum	Angio.	+
30	D. P.	3 months	III_b	Ventricular inversion	–	Pseudotruncus; PDA; double SVC	–	–	+
31	S. L.	1 week	IV	–	–	Partial pulmonary venous drainage to left innominate vein	Turner's syndrome	Angio. Cath.	–
32	J. G.	5 years	IV	–	–	–	–	Angio.	–
33	D. D.	1 month	IV	–	–	VSD; coarctation of both PA	–	Angio. Cath.	+
34	R. N.	2 months	V_a	Simple DPN	–	Single ventricle with pulmonary atresia; PDA	Severe dextrokyphoscoliosis; hemivertebrae; multiple synostoses of ribs	Angio.	+
35	I. P.	6 months	V_a	Simple DPN	–	VSD; aneurysm, pars membranea	Dextrokyphoscoliosis; horseshoe kidney; fused left upper ribs; Meckel's diverticulum	Angio.	+

Table I. Cont'd

Patient	Age*	Dextrocardia: Type	Dextrocardia: Degree†	Situs inversus	Intracardiac anomalies‡	Extracardiac anomalies	Special studies	Autopsy
36 C. W.	1 week	V_a	Simple DPN	–	Severe tetralogy; PDA	Aberrant systemic artery to right lung	Angio.	+
37 E. R.	1 month	V_b	DPN + mid-PVR	–	–	Aberrant systemic artery to right lung	Angio. Cath.	+
38 C. D.	9 months	V_b	DPN + mid-PVR	–	–	Eventration, left diaphragm	Angio. Operation	–
39 P. G.	5 years	V_b	DPN + mid-PVR	–	–	Congenital narrowing of left chest cage	Angio.	–
40 B. W.	2 days	V_b	DPN + mid-PVR	–	–	Large diaphragmatic hernia, left	Operation	–
41 B. G.	2 hours	V_b	DPN + mid-PVR	–	–	Large diaphragmatic hernia, left	Operation	–
42 B. S.	8 hours	V_b	DPN + mid-PVR	–	–	Large diaphragmatic hernia, left	–	+
43 B. W.	1 hour	V_b	DPN + mid-PVR	–	–	Large diaphragmatic hernia, left	–	+
44 B. S.	8 hours	V_b	DPN + mid-PVR	–	–	Large diaphragmatic hernia, left	–	+
45 R. B.	4 months	V_b	DPN + mid-PVR	–	–	Congenital cystic disease, left lung	Angio. Operation	+
46 J. R.	7 weeks	V_c	DPN + mid-PVR	–	–	Congenital cystic disease, left lung	Angio. Operation	–
47 S. S.	3 days	V_c	DPN + severe PVR	–	–	Bronchogenic cyst, left lung	Operation	–
48 B. A.	5 months	V_c	DPN + severe PVR	–	–	Pulmonary hypoplasia of RUL; atelectasis right lung	Angio.	–
49 S. B.	7 weeks	V_c	DPN + severe PVR	–	PDA	Hypoplasia of right lung	Angio.	+
50 F. W.	3 days	V_c	DPN + severe PVR	–	–	Aberrant systemic artery to right lung	Angio. Operation	–

*Age when dextrocardia was first noted.
†Degree of dextrocardia: C, complete; Inc., incomplete; DPN, dextroposition; PVR, pivotal rotation.
‡ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; SVC, superior vena cava.

Table II. Incidence of cardiac anomalies in the various types of congenital dextrocardia

Type	Total No. cases	No. cases with cardiac anomalies	Incidence (%)
I	11	6	55
II			
a. Complete	10	10	100
b. Incomplete	5	4	80
III	4	4	100
IV	3	2	66.5
V	17	4	23.5

studied. Situs inversus was noted clinically as well as at autopsy in all of the 11 cases with Type I dextrocardia. One of the cases with Type III dextrocardia (Case 29) had incomplete rotation of the cecum which represents a partial type of situs inversus. Whether isolated mirror-image dextrocardia, i.e., Type I dextrocardia without situs inversus of any form, occurs at all has been questioned.[9] Analysis of the previously reported cases[3, 11-15] reveals that the diagnosis of chamber inversion in some instances was based solely on the electrocardiographic findings which are certainly insufficient and that in other cases the presence of partial situs inversus was disregarded or overlooked. In one of the cases with isolated dextrocardia and chamber inversion (Case 3) reported by Lowe and McKeown[15] no abnormality of the abdominal viscera was mentioned. Since the anatomy of the 4 cardiac chambers was not described, one cannot be certain that this represents a case

Table III. Frequency distribution of various cardiac malformations encountered in congenital dextrocardia

Entities	Type I		Type II		Type III		Type IV		Type V		Relative incidence for all types	
	No.*	(%)	No.*	(%)	No.*	(%)	No.*	(%)	No.*	(%)	No.†	Incidence (%)
Tetralogy of Fallot	3/11	27	6/15	40	2/4	50	–	–	1/17	6	12/30	40
Single ventricle with pulmonary stenosis	1/11	9	1/15	6.7	–	–	–	–	1/17	6	3/30	10
Tricuspid atresia or stenosis	1/11	9	1/15	6.7	1/4	25	–	–	–	–	3/30	10
Atrial septal defect	–	–	2/15	13	–	–	–	–	–	–	2/30	6.7
Mitral stenosis or atresia	–	–	1/15	6.7	1/4	25	–	–	–	–	2/30	6.7
Partial anomalous pulmonary venous drainage	–	–	1/15	6.7	–	–	1/3	33	–	–	2/30	6.7
Complete transposition of great vessels with pulmonary stenosis	–	–	2/15	13	–	–	–	–	–	–	2/30	6.7
Ventricular septal defect	–	–	–	–	–	–	–	–	1/17	6	1/30	3.3
Ventricular septal defect with stenosis of both pulmonary arteries	–	–	–	–	–	–	1/3	33	–	–	1/30	3.3
Persistent ostium atrioventriculare commune	1/11	9	–	–	–	–	–	–	–	–	1/30	3.3
Patent ductus arteriosus	–	–	–	–	–	–	–	–	1/17	6	1/30	3.3

*Numerator refers to number of cases encountered; denominator refers to total number of cases in each type.
†Numerator refers to total number of cases; denominator refers to total number of abnormal hearts in the series.

*Age when dextrocardia was first noted.
†Degree of dextrocardia: C, complete; Inc., incomplete; DPN, dextroposition; PVR, pivotal rotation.
‡ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; SVC, superior vena cava.

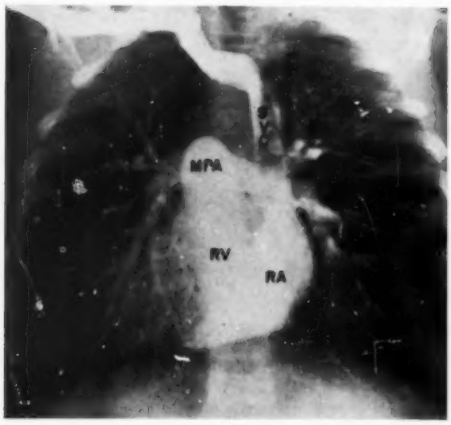


Fig. 3. (Case 5.) Mirror-image dextrocardia (Type I) with essentially normal heart. *A*, Dextroangiocardiogram, anteroposterior view. The superior vena cava *(SVC)*, right atrium *(RA)*, right ventricle *(RV)*, and pulmonary trunk *(MPA)* are situated in a reversed position of the normal.

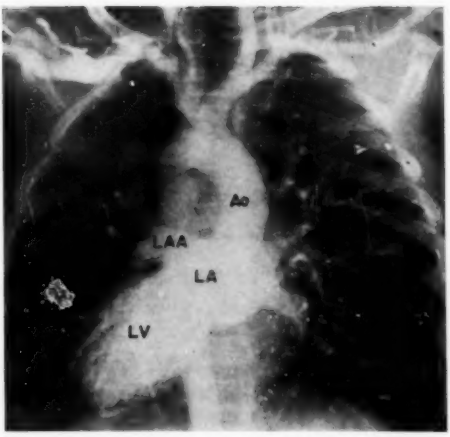


Fig. 3*C*. Levoangiocardiogram, anteroposterior view. The left atrium *(LA)* and its appendage *(LAA)*, the left ventricle *(LV)*, and the aorta *(Ao)* similarly assume a reversed position in this view.

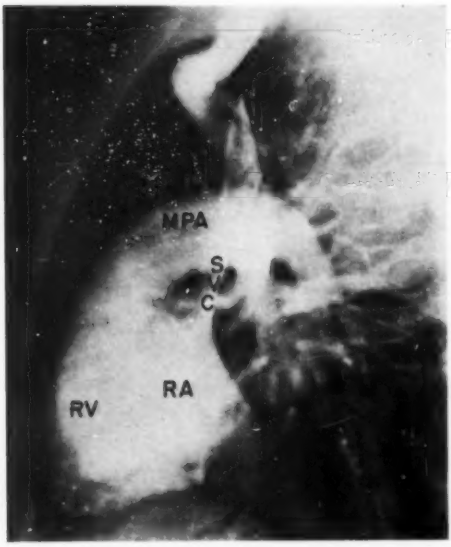


Fig. 3*B*. Lateral view of same, showing normal location of these chambers and vessels.

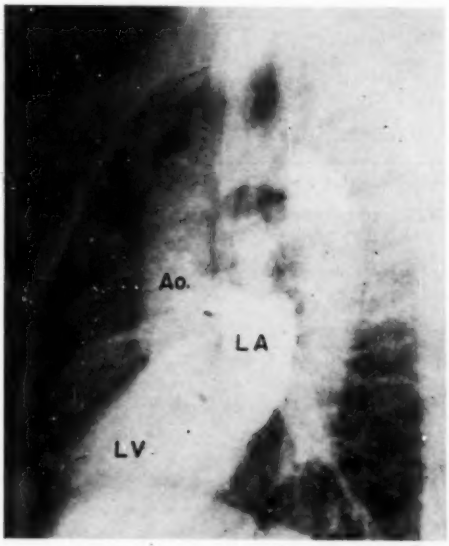


Fig. 3*D*. Lateral view. Same structures normally situated behind their corresponding venous chambers.

of isolated mirror-image dextrocardia. In the other 3 cases supposedly belonging to the same category, partial situs inversus was present. We believe that all of the reported cases of isolated mirror-image dextrocardia really represent either Type II or possibly Type III dextrocardia.

Of the 20 cases studied at autopsy, 10 belonged to the intrinsic group (Types I, II, III, and IV) of dextrocardia. Asplenia

was noted in 2 patients (Cases 7 and 29). One of the patients with Type V dextrocardia (Case 35) had a horseshoe kidney and Meckel's diverticulum. The true incidence of intra-abdominal congenital anomalies cannot be ascertained in our study since only 40 per cent of the series came to autopsy.

Congenital anomalies of the diaphragm, of the lungs, and of the chest wall were noted only in the group with extrinsic dextrocardia (Type V). Large diaphragmatic hernias were present in 5 newborn infants. One patient (Case 38) had marked eventration of the left diaphragm. Congenital anomalies of the lungs were seen in 8 patients. Aberrant systemic arteries arising from the descending aorta and from an anomalous right subclavian artery supplying the right lung were noted in 3 patients (Fig. 2). Congenital cystic disease of the left lung was present in 3 other cases. In 2 patients hypoplasia of the right lung was found. Severe skeletal deformities involving the spine and ribs accounted for the cardiac displacement in 3 patients.

The association of congenital extrinsic dextrocardia with anomalies involving the arterial supply and/or the venous return of the right lung is not well known. Of the many cases of aberrant systemic arteries to the lung previously reported[16, 17] the occurrence of associated dextrocardia has been described in only 6 cases.[16, 18-20] Extrinsic dextrocardia has also been reported in association with anomalous pulmonary venous drainage of the right lung into the inferior vena cava.[20-28] A striking finding in these reports, as well as in our 3 proved cases with aberrant systemic arteries supplying the right lung, is the smaller caliber of the right pulmonary vessels and the over-all diminution in size of the right lung. This hypoplasia of the vascular bed and of the parenchyma of the right lung probably accounts for the displacement of the mediastinum.

The incidence of cardiac anomalies in our series is summarized in Table II. It is of interest to note that, whereas a majority of workers[2, 15, 29-31] have reported normal cardiac findings in most cases of Type I dextrocardia, 6 of the 11 cases in our series had multiple cardiac malformations. Others,[32-34] however, have reported findings similar to ours. Since these anomalies are severe and

Fig. 4. (Case 21.) Complete dextroversion Type IIa with transposition of the great vessels, pulmonary stenosis, and ventricular septal defect. The patient had previous left subclavian-pulmonary artery anastomosis. *A*, Dextroangiocardiogram, anteroposterior view. The aorta *(Ao)* arises from the right ventricle *(RV)* and lies to the right of the pulmonary artery *(PA)*. The latter is opacified through the left subclavian artery (see arrow).

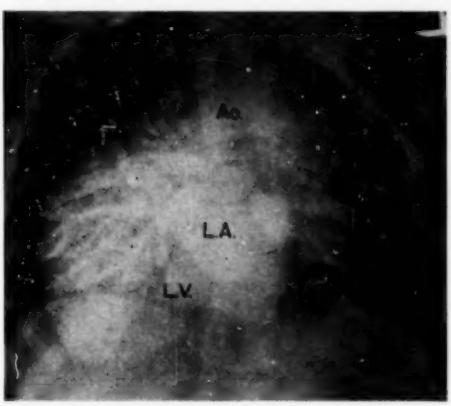


Fig. 4*B*. Levoangiocardiogram, anteroposterior view. The left atrium *(LA)* is at the midline. The left ventricle *(LV)* is situated to the left of and somewhat inferior to the right ventricle.

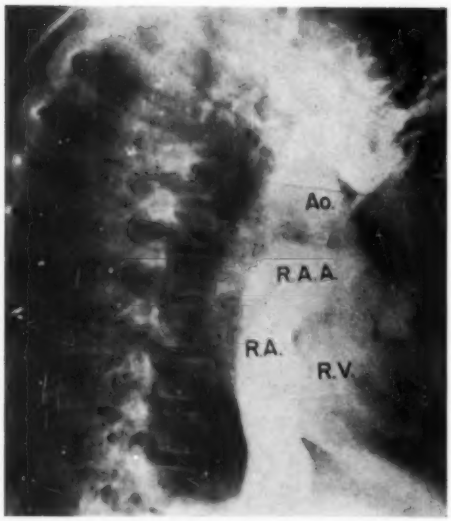


Fig. 4*C*. Repeat study in the left anterior oblique (LAO) view demonstrating the posterior location of the right atrium *(RA)* and right ventricle *(RV)*. Note posterior location of aorta *(A_o)* as it arises from the right ventricle.

most of the patients die in infancy or early childhood, this discrepancy in the reported incidence of complicated Type I dextrocardia may be due to the different ages of the patients studied. The previous reports [2, 15, 29, 30] were based mostly on findings in older children and adults.

The cardiac anomalies encountered were, as a rule, multiple and together formed specific anatomic syndromes characterized clinically by dextrocardia, cyanosis, diminished pulmonary bloodflow, and usually by right ventricular hypertrophy. The frequency of each of these morphologic complexes in the various types of dextrocardia are listed in Table III. Of the 7 autopsied cases with tetralogy, severe puulmonary stenosis was present in 3, and pulmonary atresia (pseudotruncus) in 4 cases. In 6 other cases with a similar clinical diagnosis, the angiocardiograms revealed severe pulmonary stenosis and early opacification of the aorta. Our findings are of special interest since the incidence of tetralogy in congenital dextrocardia, particularly in Type I dextrocardia, has been emphasized by Keith and coworkers[9] to be extremely unusual. They indicated that an authentic case of Type I dextrocardia with tetralogy has yet to be published. Case 7 of our series is a proved case. Autopsy studies revealed dextrocardia with situs inversus, chamber inversion of the atria and of the ventricles, a large ventricular septal defect, an atrial septal defect of the secundum type, pulmonary in fundibular stenosis, and gross overriding of the aorta. This case is also interesting because asplenia was noted; its incidence in mirror-image dextrocardia is extremely rare.[35] The diagnosis of tetralogy in 2 other cases (Cases 8 and 9) classified as Type I dextrocardia, both of which have had angiocardiographic studies, is, however, unconfirmed by necropsy.

Severe cardiac anomalies were present in all of the 10 patients with complete dextroversion (Type IIa) and in 4 of the 5 with incomplete dextroversion (Type IIb). Three cases that came to autopsy (Cases 12, 13, and 25) had large ventricular septal defects,

Fig. 5. (Case 19.) Complete dextroversion (Type IIa) with single ventricle, atrial septal defect, and pulmonary stenosis. *A*, Dextroangiocardiogram, anteroposterior view, with the contrast substance still confined in the atria. Note opacification of right atrium *(RA)* and left atrium *(LA)*, and of the right *(RSVC)* and left superior venae cavae *(LSVC)*.

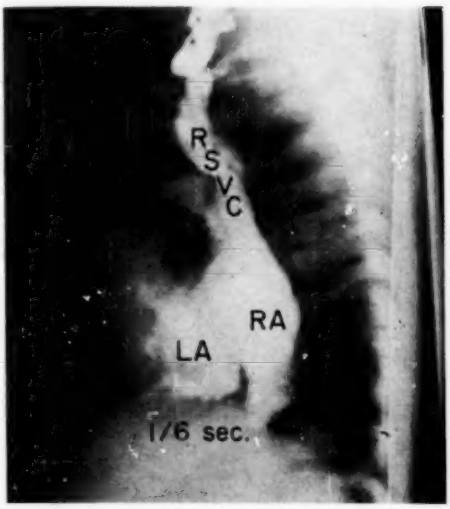


Fig. 5*B*. Lateral view of same demonstrating the anterior location of the left atrium *(LA)*.

pulmonary atresia or severe pulmonary stenosis, and dilated overriding aorta. The very high incidence of severe cardiac malformations in dextroversion, about 80 per cent having anomalies of the outflow tract, and that of transposition of the great vessels are well known.[3, 8, 25] Although cases of so-called isolated dextrocardia with functionally normal hearts have been reported,[5, 31, 35-41] a review of these articles indicates that the majority probably were incomplete dextroversion or mesoversion. The autopsied case described by Aren[5] and those with angiocardiographic studies reported by Burchell and Pugh (Case 1),[31] Grant (Case 3),[35] and Welsh and Felson (Case 7)[40] are typical examples of mesoversion. In the other cases where angiocardiography or autopsy studies were not performed, the cardiac configuration in the chest roentgenograms was compatible with that of mesoversion. This observation suggests that, whereas complete dextroversion is almost always associated with severe cardiac anomalies, mesoversion is not necessarily so. One of our 5 cases of mesoversion had no clinical and angiocardiographic evidences of any cardiac defect (Case 22). Four patients with mixed dextrocardia (Type III) had severe cardiac anomalies, and all but one died during infancy. A patient with congenital dextroposition (Type IV) had partial anomalous left pulmonary venous drainage into the left innominate vein and another had a small ventricular septal defect and coarctation of both pulmonary arteries.

ANGIOCARDIOGRAPHIC FINDINGS

Since the heart is a three-dimensional organ, the angiocardiogram recorded simultaneously in 2 planes offers the best information regarding the position of the atria, ven-

Fig. 6. (Case 28.) Mixed dextrocardia (Type IIIb) with right atrioventricular atresia, atrial and ventricular septal defects, pulmonary atresia, and patent ductus arteriosus. *A*, Angiocardiogram, lateral view. The superior vena cava *(SVC)* enters the right atrium *(RA)* which communicates with an anteriorly situated left atrium *(LA)*. From the left atrium, the dye opacifies an anterior ventricle *("RV")* which was identified at necropsy as the right ventricle from which the aorta arises.

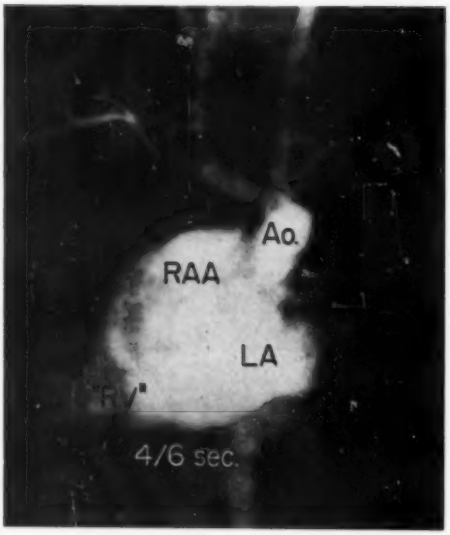
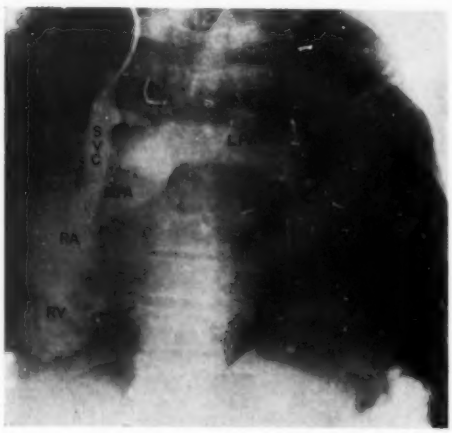
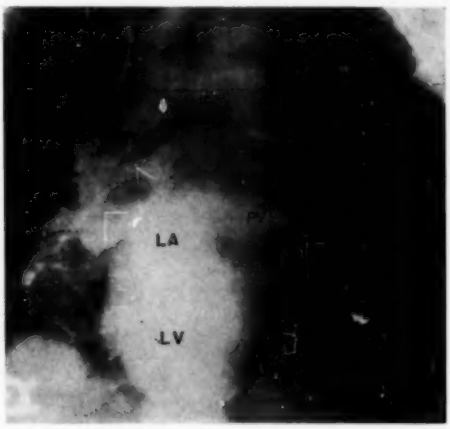


Fig. 6*B*. Anteroposterior view showing the position of the left atrium *(LA)* to the left of the right atrium *(RA)*. The anatomic right ventricle *("RV")* occupies the usual location of the left ventricle in this type of dextrocardia.

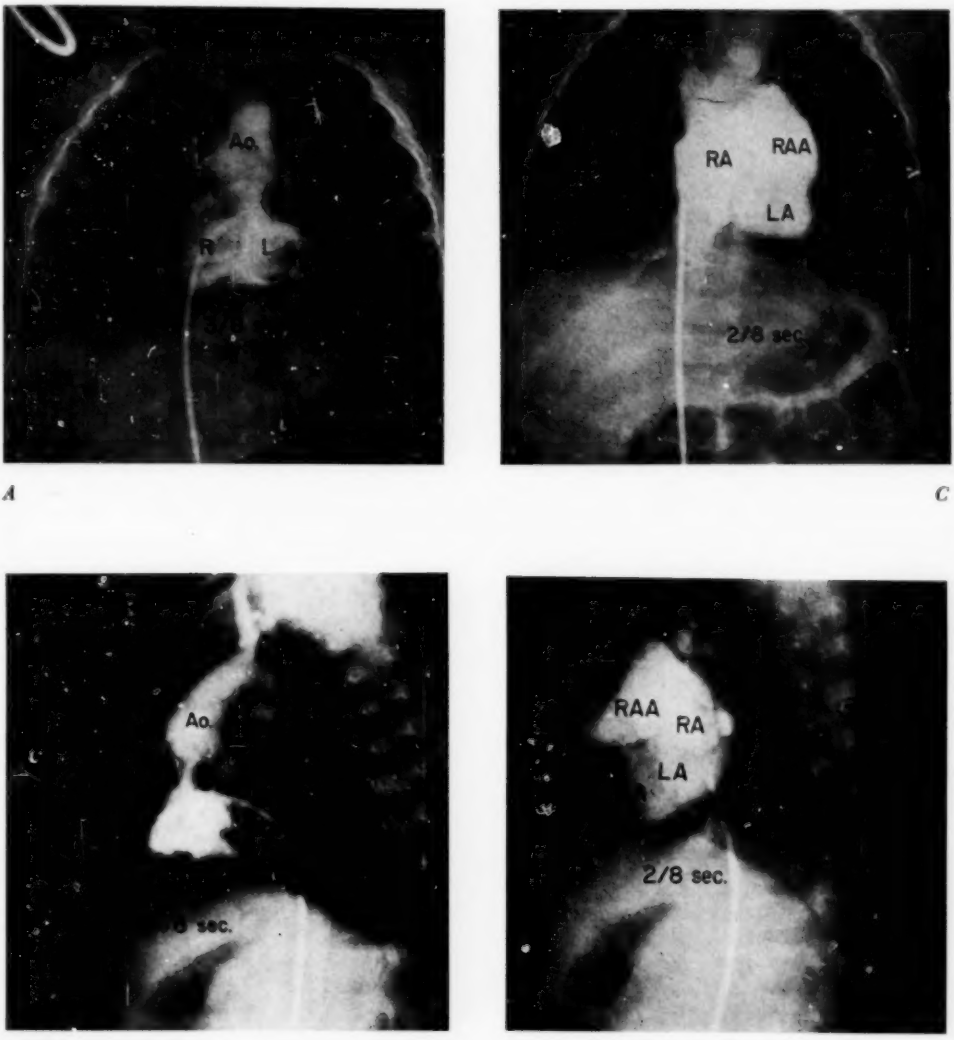
tricles, and great vessels. One is thus able to determine which chamber and which vessel are situated anteriorly or posteriorly and to the right or left. The angiocardiogram taken simultaneously in 2 planes is a better index of the true position of the heart than that noted even at the autopsy table because alterations in the position of the heart during the various phases of the respiratory and cardiac cycles are then discernible. Conventional roentgenologic examinations, even if taken in multiple views, are far from satisfactory because it is impossible to differentiate accurately the cardiac chambers and great vessels from one another. The electrocardiogram is similarly only partially informative because of inherent intrinsic and extrinsic factors that modify the tracings, particularly in the presence of ventricular hypertrophy. The configuration of the P wave, however, is most helpful in indicating the position of the atria. While the angiocardiogram is thus superior to any other method for studying the position of the heart, it may at times be inadequate for identifying the individual anatomic chambers. The right ventricle can be differentiated from the left one, if the contrast substance demonstrates the presence of the crista supraventricularis and of the septal and parietal bands which are absent





A *B*

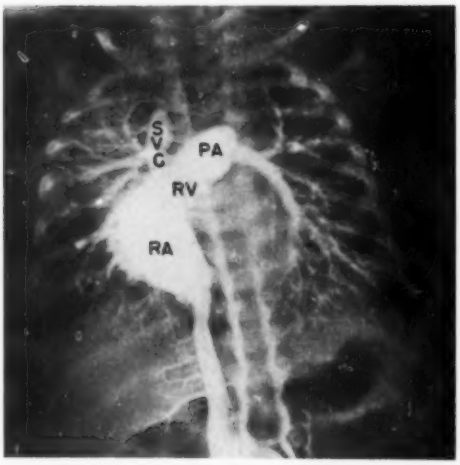
Fig. 7. (Case 22) Incomplete dextroversion (Type IIb) with a normal heart. *A*, Dextroangiocardiogram, anteroposterior view. The right atrium *(RA)* and right ventricle *(RV)* are nearly completely superimposed in this view. Note medial location of outflow tract and the unfolding of the left pulmonary artery *(LPA)*. *B*, Levoangiocardiogram, anteroposterior view. The left atrium *(LA)* and left ventricle *(LV)* are similarly superimposed.



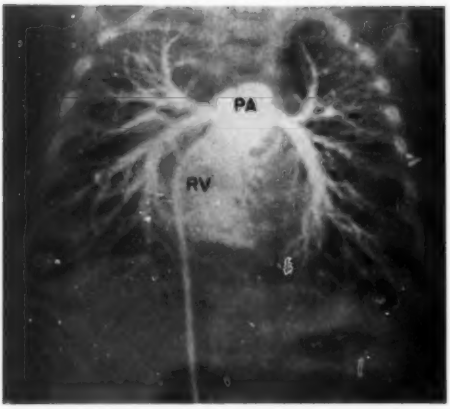
A C

B D

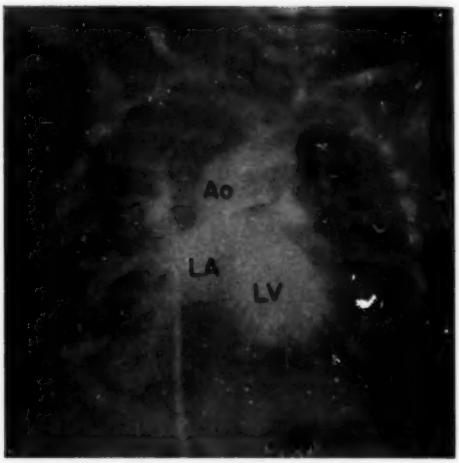
Fig. 8. (Case 25.) Incomplete dextroversion (Type IIb) with a large ventricular septal defect, atrial septal defect, overriding aorta, pulmonary infundibular stenosis, and juxtaposed atrial appendages. *A*, Anteroposterior view. Selective injection of contrast substance into the right ventricle with immediate opacification of the right *(RV)* and left *(LV)* ventricles and no identifiable septum. Small pulmonary artery *(PA)* arises from the right ventricle through an infundibular stenosis (see arrow). The aorta is at the midline and originates mostly from the left ventricle. *B*, Lateral view of same showing the anterior and superior location of the aorta compared to the pulmonary artery. Arrow points to infundibular stenosis. *C*, Anteroposterior view. Selective injection of contrast substance into the right atrium with immediate filling of the right *(RA)* and left *(LA)* atria. Note abnormal location of right atrial appendage *(RAA)* on the left side and above the left atrial appendage *(LAA)*. *D*. Lateral view demonstrating the abnormal position of the atrial appendages. The 2 atria are situated well behind the still unopacified ventricular chambers.



A



B



C

Fig. 9. (Case 33.) Congenital dextroposition (Type IV) with small ventricular septal defect and coarctation of both main pulmonary arteries. *A*, Peripheral venous angiocardiogram, anteroposterior view. The right atrium *(RA)* and right ventricle *(RV)* occupy the right thoracic cavity. Note unusual direction of outflow tract. *B*, Selective injection of contrast substance into outflow tract, anteroposterior view. The right ventricle *(RV)* is somewhat medial to the right atrium. Note small main pulmonary arteries compared to the pulmonary trunk *(PA)*. *C*, Levoangiocardiogram, anteroposterior view, showing normal relations of the left atrium *(LA)* and left ventricle *(LV)*. The aortic arch is wider than normal.

in the left ventricle. Since the entrance of the systemic and pulmonary veins may be transposed in patients with congenital malformations of the heart, the only way to differentiate the right from the left atrium is to note the presence of the limbus and fossa ovalis in the former. Angiocardiography cannot now demonstrate these structures.

TYPE I DEXTROCARDIA (MIRROR-IMAGE DEXTROCARDIA)

The contrast substance enters the heart via the superior vena cava on the left side (Fig. 3*A*). The venous atrium is the anatomic right atrium situated to the left of and anterior to the anatomic left atrium. The venous and anatomic right ventricle is similarly located to the left of and anterior to the anatomic left ventricle. Its outflow tract is situated to the right of the inflow tract. The atrial appendages are in a reversed position in the anteroposterior view. The main pulmonary artery is located anteriorly as it normally is (Fig. 3*B*), but it lies immediately to the left of the aorta over which it crosses as it goes to the right side. The position of the

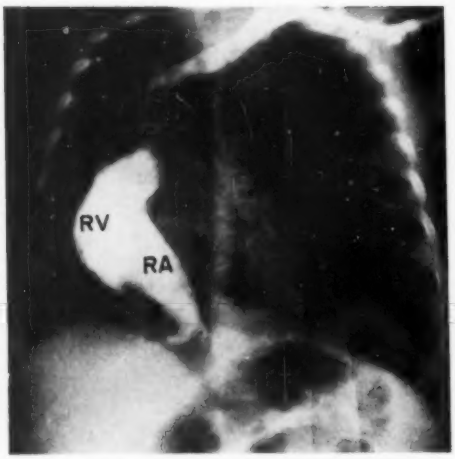
aorta is similarly reversed in the anteroposterior view (Fig. 3*C*). A right aortic arch was present in 10 of our 11 cases. Whereas the positions of the cardiac chambers and great vessels are reversed in the frontal plane (Figs. 3*A*, 3*C*), their locations in the sagittal plane as seen in the lateral or oblique views are normal (Figs. 3*B*, 3*D*). There is truly an anatomic inversion of the corresponding chambers, which produces an arrangement that is a mirror-image of the normal.

TYPE II DEXTROCARDIA (DEXTROVERSION COMPLEX)

As illustrated in Fig. 1, dextroversion may be complete (Type IIa) or incomplete (Type IIb) depending upon the degree of heterotaxy. Gubbay[38] described two forms of dextrocardia: (1) the "obliquely placed isolated dextrocardia" which corresponds to complete dextroversion, and (2) the "vertical isolated dextrocardia" which corresponds to mesoversion. In describing the position of the heart with this type of dextrocardia, Gubbay[38] and Chapman and Gibbons[39] stated that the venous or right atrium is situated superiorly and to the right while the "inflow tract of the venous ventricle passes downward to the right and backward and the outflow tract then turns upward." Our findings did not exactly tally with this description. The venous ventricle has also been described, and this we have corroborated to be located posterior and superior to the arterial ventricle.[35, 38] The term "vertical isolated dextrocardia" for mesoversions is a misnomer because, although the heart appears to be vertically suspended in the posteroanterior chest roentgenograms, anatomically it is in a more horizontal position than is the normal heart.

Complete dextroversion. The angle in the horizontal plane formed by the longitudinal axis of the heart with the midsagittal axis of the chest is around 30 to 40 degrees to the right. The contrast substance enters the anatomic right atrium via the right superior vena cava which is usually located medially. The opacified right atrium is partially superimposed on the right ventricle in the anteroposterior view with the inflow tract of the right ventricle directed downward to the right and anteriorly. The outflow tract is directed posteriorly, superiorly, and medially (Fig. 4*A*). The left atrium is at the midline, to the left of and slightly anterior to the right atrium (Figs. 5*B*, 6*A*). The left ventricle is situated anteriorly, inferiorly, and to the right of the left atrium. It is also anterior to, to the left of, and inferior to the right ventricle (Figs. 4*B*, 4*C*). The position of the great vessels in complete dextroversion deserves special comment. From Lichtman's[3] excellent review of the so-called isolated dextrocardia it is apparent that, in the reported cases where the 2 ventricles were identified, the anteriorly located aorta arose from the anteriorly situated left ventricle; the posteriorly located pulmonary artery, from the posteriorly located right ventricle. Because of the reversed anteroposterior relationship of the great vessels the incorrect diagnosis of transposition of these vessels has thus been made. In some instances, the term "corrected transposition"[9, 42] has been used in referring to this condition which actually does not fit any of the various types of corrected transpositions so well described by Anderson and colleagues.[43] Since the anteroposterior relationship of the 2 ventricles is reversed, the aorta, as it originates from the left ventricle, lies anteriorly to the pulmonary artery and this does not necessarily denote transposition of these vessels. In 3 cases that came to autopsy as well as in 7 cases studied by angiocardiograms where the 2 major vessels were identifiable the aorta was situated to the left of and anterior to the pulmonary artery in the absence of complete transposition (Fig. 6*A*), whereas in complete transposition of these vessels, the aorta is located to the right of and somewhat posterior to the pulmonary artery (Figs. 4*A*, 4*C*). A left aortic arch was present in 8 of our 10 cases.

Most authors[1, 3-8] have shown that the atria maintain their normal position in the frontal plane but not in the sagittal plane



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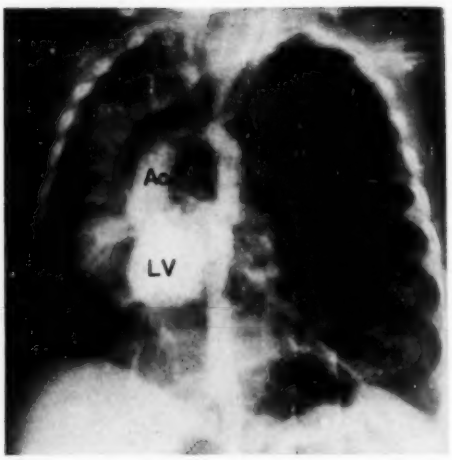

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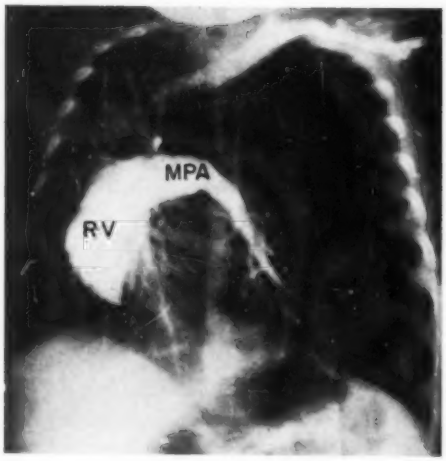

B

Fig. 10. (Case 46.) Congenital extrinsic dextrocardia (Type V) with dextroposition and midpivotal rotation. Peripheral venous angiocardiogram, anteroposterior view. *A*, Contrast substance still confined in right atrium *(RA)* and right ventricle *(RV)*. Note marked displacement of superior vena cava *(SVC)* and of right ventricle *(RV)* laterally. The apex of the right ventricle points anteriorly. *B*, The outflow tract of the right ventricle *(RV)* is located medially and continues into the pulmonary trunk *(MPA)* which bifurcates at the midline. Note unfolding of left pulmonary artery. *C*, Levoangiocardiogram demonstrating the superimposed left atrial and left ventricular *(LV)* chambers. Note wide aortic arch *(Ao)*.

since the left atrium is anterior to the right atrium, an arrangement similar to that assumed by the 2 ventricles. Grant,[35] however, emphasized that while the left ventricle is more anteriorly located than the right ventricle, the left atrium remains to the left of and posterior to the right atrium. In our 2 autopsied cases as well as in those where angiocardiograms were taken in the anteroposterior and in the lateral or oblique views, the left atrium was at the midline and to the left of and slightly anterior to the right atrium (Figs. 5, 6). The position of the cardiac chambers may be appreciated by imagining the ventricles of a normally situated heart to have undergone a rightward pivotal rotation of about 90 degrees around a posteriorly located vertical axis accompanied simultaneously by a 45 degree clockwise rotation at its longitudinal axis. The rightward rotation of the atria is of a comparatively lesser degree, possibly because of the anchoring effect of the venae cavae and of the pulmonary veins.

Incomplete dextroversion (mesoversion). The 5 cases (Cases 22 to 26) in this cate-

gory demonstrate the typical findings in mesoversion. The longitudinal axis of the heart and the interventricular septum are along the midsagittal axis of the chest. In the posteroanterior view, the position of the cardiac chambers is similar to that of a normal left anterior oblique view of 45 to 50 degrees.

The contrast material enters the right atrium by way of the superior vena cava situated normally or slightly posteriorly. The right atrial chamber overlaps the right ventricle in the anteroposterior view, but these 2 chambers are well separated in the lateral view. The outflow tract is located medially and continues into the main pulmonary artery which bifurcates in the midline into the right and left main branches. The left pulmonary artery is unfolded in the anteroposterior view, while the main and right pulmonary arteries are situated behind the right heart chambers (Fig. 7*A*). The left atrium is at the midline and is similarly superimposed on the left ventricle which lies anterior and slightly inferior to it. Its outflow tract is medially situated and continues into the aorta which usually has a left arch (Fig. 7*B*). As seen in the lateral view, the heart is more horizontally situated than it normally is. The heart size appears narrow in the frontal view but wider in the lateral view, since in the latter view the plane of the observer is at right angles to the main heart axis (Fig. 8).

Anatomically, the position of the heart is nearly similar to that noted in complete dextroversion with the difference that the rotation is not as marked and is terminated when the longitudinal axis of the heart is nearly parallel to the midsagittal axis of the chest. The cardiac apex is located substernally, and the right and left ventricles lie to the right and left of the sternum, respectively.

TYPE III DEXTROCARDIA (MIXED DEXTROCARDIA)

In rare instances, chamber inversion may occur involving only the atria (mixed dextrocardia with atrial inversion) or only the ventricles (mixed dextrocardia with ventricular inversion) with or without an accompanying transposition of the great vessels. This unusual type of dextrocardia has been reported under various names like "mirror picture transposition of the ventricles and great arterial trunks,"[12] "corrected transposition of the great vessels with dextrorotation of the heart,"[14] or "corrected transposition of the great vessels with mirror-image dextrocardia"[44] when it is associated with complete transposition of the great vessels. The angiocardiographic findings in mixed dextrocardia resemble those described in complete dextroversion when ventricular inversion is present (Fig. 6) or resemble those noted in complicated cases of mirror-image dextrocardia when atrial inversion is present. As previously stated the morphologic differentiation of the right from the left ventricle by selective angiocardiography is possible only if the crista supraventricularis and its parietal and septal bands are demonstrated in the right ventricle. The identification of either atrium by contrast radiography alone is not possible. However, when a superior vena cava enters a venous atrium on the left side and there are electrocardiographic findings of inverted P waves in Lead I and in the left precordial leads, atrial inversion is almost always present. When these findings are not associated with situs inversus, mixed dextrocardia (Type IIIa) should be strongly suspected.

TYPE IV DEXTROCARDIA (CONGENITAL DEXTROPOSITION)

Congenital dextroposition is another rare form of dextrocardia. Korth and Schmidt[45] and Flehmig and Priess[46] have each reported a case of "essential dextroposition" on the basis of the clinical, roentgenologic, and electrocardiographic findings. The arrangement of the cardiac chambers was, however, not demonstrated by means of angiocardiographic or autopsy studies.

The heart is situated medially, more in the right than in the left thoracic cavity

(Fig. 9). The various cardiac chambers are outlined in a normal fashion, and, the apex, although it is still directed anteriorly and to the left, lies closer to the midline. The arch of the aorta appears wider than normal in the frontal plane, probably as a result of the rightward location of the heart and of the ascending aorta. The position of the heart is that which it would assume if it were shifted en masse to the right along the frontal plane.

TYPE V DEXTROCARDIA (CONGENITAL EXTRINSIC DEXTROCARDIA)

The cases belonging to this category represent a distinctly different group from those previously described, since the abnormal position of the heart is due to the extracardiac anomalies of the chest previously described (Table I). In simple dextroposition, the position of the cardiac chambers and of the great vessels as well as the lateral displacement of the heart and of the superior vena cava resembles the pattern in congenital dextroposition. In the 14 cases where the extrinsic dextroposition was accompanied by varying degrees of pivotal rotation in the horizontal plane, the superior vena cava was displaced not only laterally but also posteriorly. In the anteroposterior view, the right atrium and right ventricle as well as the left atrium and left ventricle overlap each other, respectively, in varying degrees depending upon the extent of the pivotal rotation. The left atrium and left ventricle remain to the left of the right heart chambers. The position of the pulmonary trunk and the unfolding of the left pulmonary artery in the anteroposterior view resemble the patterns described in complete or incomplete dextroversion while the laterally situated superior vena cava and the unusually wide left aortic arch are similar to the changes noted in congenital dextropositions (Fig. 10).

(The second part of this article will appear in the February issue.)

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Conjoined thoracopagus twins

Pre- and postoperative considerations

Allan J. Hill, Jr., M.D.,* Clare G. Peterson, M.D.,

Raymond D. Grondahl, M.D., and William W. Krippaehne, M.D.

PORTLAND, ORE.

CONJOINED twins (diplopagus) are presently believed[1] to result from incomplete fission of monovular twins. They usually are nearly symmetrical, with the bridge of tissue uniting them situated between their heads, thoraces, abdomens, or pelves. The union is most commonly central and ventral, but it may be polar, dorsal, or lateral.[2] The term diplopagus implies that the twins are normal except for the junction. The bridge, however, may consist of merely superficial tissue easily separated[3, 4, 5] and unassociated with severe anomalies, or it may include single organs shared by both partners. When the bridge is ventrally located and includes both thorax and abdomen (thoracoomphalopagus), organs which may be common to both twins include the heart,[6, 7, 8] the intestinal tract,[9-13] and the liver.[1, 8, 14] Furthermore, serious anomalies may be present in organs other than those constituting the bridge.[1, 7, 13, 15] While one might anticipate situs inversus in some separate monovular twins (22 per cent), 73 per cent of conjoined twins demonstrate one to be the mirror image of the other.[16] The union may be so extensive that one twin is completely parasitic upon the other.[17, 18]

Because conjoined twins are rare, appearing at the approximate rate of one for every 50,000 deliveries,[1] because each instance seems to have peculiarities of its own, and because surgical separation has become increasingly successful, the following report of thoracoomphalopagus twins is offered in some detail. Thoracopagus twins are apparently the most common variety of diplopagus, appearing once in about 82,000 deliveries; female thoracopagus twins are from two to three times as frequent as males.[6]

PREOPERATIVE PROGRESS

In Nyssa, Oregon, on June 29, 1959, thoracoomphalopagus twins were born by cesarean section to Mrs. C. S., aged 24 years, gravida iv, para iii, and Mr. J. S., aged 25. The siblings were a 4-year-old boy, a 2½-year-old girl, and a 1½-year-old girl. There had been three sets of separate twins: the maternal great-grandmother had twin brothers and the maternal grandmother's brother and sister each had one set of twins. The mother had been well except during the fifth week of pregnancy, when

From the Departments of Pediatrics, Surgery, and Clinical Pathology, University of Oregon Medical School.

**Address, 3181 S.W. Sam Jackson Park Road, Portland 2, Ore.*

she had severe gastric cramping which lasted 2 to 3 days, and except for an 8½-pound gain in weight during the latter third of her pregnancy, associated with mild edema, transient mild proteinuria, and slight hypertension. Although twins had been discovered radiographically at 5½ months of gestation, the true nature of the pregnancy was not revealed until birth. The anticipated date of confinement was July 23, 1959. At the thirty-sixth week of gestation, with a double breech presentation, medical induction of labor was instituted. Because there was no progress, cesarean section under local anesthesia was undertaken and the nature of the difficulty was disclosed. There was moderate polyhydramnios, and a single umbilicus, cord, and placenta. The twins breathed promptly and spontaneously; they were vigorous and responsive. Their combined weight was 4.29 kilograms, and the crown-heel length of each was 43 cm. After preliminary feedings of glucose water, the twins at 22 hours of age were transferred by airplane to the University of Oregon Medical School Hospital.

A large bridge of tissue joined the twins from the fifth costal cartilages to a common umbilicus (Fig. 1). J. had a small tag of skin immediately anterior to her right ear; D. had no other visible anomaly. The maximum head circumferences were 33.5 cm. at birth, 35.5 cm. at 1 month, and 38 cm. at 2 months of age, respectively. Both twins were mildly cyanotic in the periphery of the lower extremities. The heart and respiratory rates were dissimilar. D.'s spleen could be palpated 1 cm. below the left costal margin, and the nonbony portion of the bridge obviously contained tissue which was presumed to be liver. Both twins had unsustained ankle clonus which persisted up to 2½ months of age.

Their course up to the time of separation at 3 months of age (Oct. 6, 1959) was generally favorable. The temperature, pulse, and respiration had stabilized by the third day. Oral feedings of a standard formula for premature infants were taken well and growth was both steady and satisfactory (Table I). Their minimum combined weight, reached on the third day, was 3.95 kilograms. Vitamins A, B complex, and D were begun during the first week, and a vitamin C supplement was added during the second. Puréed foods were taken without difficulty by the twins when they were 6 weeks old, and intramuscular iron was given when they were 2½ months old. Their hemoglobin level steadily fell from 19.5 Gm. per 100 c.c. of blood at 1 day of age to 9.6 Gm. at 2½ months. The plasma proteins at 3 months were 6.3 Gm. per 100 c.c., with 4.4 Gm. of albumin and 1.9 Gm. of globulin. D.'s activity and intake of food were more vigorous than those of J., although the latter twin appeared to be larger. Their common umbilical stump contained three vessels, and from the third to the ninth day developed an infection with Pseudomonas and nonhemolytic Staphylococcus organism, which responded satisfactorily to intramuscular penicillin and streptomycin. Subsequently each was given weekly 2 c.c. of gamma globulin intramuscularly. During

Fig. 1. External view of twins at 3 months of age (J. on right).

Table I. Growth for 6 months

Date (1959)	Age (months)	J. Height (cm.)	J. Weight (Kg.)	Combined weight (Kg.)	D. Height (cm.)	D. Weight (Kg.)
7/ 1	0	43.0		4.07	42.5	
7/16	½	45.0		4.87	44.5	
7/29	1	49.5		5.73	50.0	
8/13	1½			6.70		
8/31	2	53.0		7.38	53.5	
9/17	2½	53.25		8.13	54.0	
9/26	3	54.0		8.40	54.5	
10/ 6	Operation					
11/10	4	54.0	5.46		57.5	4.97
11/28	5	54.0	6.01		58.5	5.18
12/23	6	58.5	6.52		59.7	5.57

their third week they developed a mild mucoid rhinorrhea from which Pseudomonas and nonhemolytic Staphylococci were recovered and a mild oral infection with *Candida albicans.*

During the first week it became apparent that the twins would survive unseparated. Surgical division was delayed for several reasons: (1) the hazards of anesthesia and operation during the newborn period and (2) the advantages of time for disclosing serious hidden anomalies and for permitting unhurried studies. The chief disadvantage in delay was thought to be the increasing difficulty with mobilization of skin flaps to cover the extensive thoracoabdominal defect. Indeed, this was the case. Retrospectively, had the twins been much older than 3 months, there is serious doubt whether the radical mobilization of skin could have been realized. On July 29, when they were 1 month old, the bridge's circumference measured 33 cm., by August 31, 35.5 cm., and by September 18, 37.5 cm.

PRE- AND POSTOPERATIVE SPECIAL STUDIES

Electrocardiographic studies (Dr. James E. Odell). Prior to operation, electrocardiograms from each twin demonstrated separate electrical activity; J.'s heart rate was faster than D.'s. Before and after separation, the P-R intervals were between 0.08 and 0.09 second, the QRS durations between 0.04 and 0.05 second, and the Q-T intervals between 0.23 and 0.26 second. J.'s mean electrical QRS axis shifted from +135° when she was 6 weeks old to +90° when she was 5½ months old, and it was always somewhat anteriorly directed. Her mean T vector shifted from +45° to +75°, and also was slightly anterior in direction. D.'s mean QRS vector was at +115° when she was 6 weeks old, with the mean T at +75°. When she was 4½ months old, her mean QRS vector had reached +95° and was anterior in direction, whereas the T vector shifted slightly leftward to +20° and was somewhat posteriorly directed. All tracings were considered to be within the extreme limits of normal for age.

Radiologic studies (Dr. Vincent C. Hinck). On June 30, 1959, a lateral film of the conjoined twins demonstrated no significant abnormality (Fig. 2) other than the soft tissue bridge which extended from the lower end of the sternum to the umbilical region. The visible portions of the sterna, although not joined, did curve ventrad, suggesting congenital fusion. The possibility of a common liver could not be excluded. Intestinal gas shadows of the two abdominal cavities were in close approximation. A lateral cone-down view of the soft tissue bridge (August 31) suggested that the loops of the bowel crossed the midline below the liver. Again, a line of cleavage between two livers could not be defined.

On Aug. 31, 1959, an intravenous pyelogram was made. Three minutes after the

injection of 7 c.c. of Miokon into D., there was homolateral visualization of both renal collecting systems and the bladder. Six minutes after injection, J.'s pelvocalycine system and bladder were visualized as well. By 9 minutes, good visualization was evident in each twin. The configuration and position of both upper and lower urinary systems appeared to be normal.

Intravenous cholangiography was performed on Sept. 1, 1959. J. was injected with 2.2 c.c. of 52 per cent Cholografin. There was faint visualization of both gall bladders in 15 minutes; each structure appeared to be normal and each was situated from 2.0 to 2.5 cm. from the soft tissue junction.

An upper gastrointestinal series and study of the small bowel was done on September 3. Previously, carmine had been administered orally to J., and this dye was recovered only in J.'s stool. Consequently, the gastrointestinal study was performed on D. Esophageal and gastric dynamics were unremarkable. The stomach had a more horizontal position than usual and the antral part of the greater curvature was situated near the bridge. The progress of the barium was followed intermittently. At fluoroscopy, it was noted that, when the children cried, the barium-filled small bowel moved back and forth across the abdominal bridge in the direction of lower intra-abdominal pressure. Clearly, there was continuity between the abdominal cavities. On the other hand, the barium did not cross to the intestinal lumen of the conjoined twin. The study was discontinued when all barium appeared to be in the colon.

Radioisotopic studies (Dr. Tyra T. Hutchens). External measurement of gamma rays by scintillation detectors permitted study of circulatory dynamics in vivo. I^{131}-labeled human serum albumin was used to acquire three types of information: (1) rate of exchange of blood between the twins, (2) blood and plasma volumes, and (3) location of any major vascular communication. The twins were lying on their sides, with a distance of 10 inches between their exposed ears. It had been determined earlier that a 10 inch separation between detectors would obviate cross-recording; minor differences in sensitivities of the two detectors had already been ascertained. Background rates were counted immediately before and immediately after the procedure. Two-by-two-inch crystal scintillation detectors with approximately 30-degree collimation were centered vertically over and in contact with the uppermost ear of each twin. Each of the detectors was attached to a separate single-channel gamma-ray spectrometer, decade scaler and elapsed-time timer, count rate meter, and continuous graphic recorder.

Fig. 2. Full-body lateral roentgenogram at 1 day of age.

On September 8, 1 c.c. of saline solution which contained approximately 30 μc of I^{131}-labeled human serum albumin was injected into a scalp vein as rapidly as possible. After injection, the two continuous recorders demonstrated graphically that the maximum rate over the injected twin's head dropped rapidly to plateau in about 10 minutes, whereas the rate over the uninjected twin's head started at zero, rose rapidly, and also reached a plateau in approximately 10 minutes. Because the injection of labeled albumin was not instantaneous, the typical parabolic curves did not appear until about 2 minutes after injection.

Plotted on semilogarithmic paper, the recorded scaler counts approximated exponential curves after the first few minutes, whereas the continuous graphic chart counts failed to conform as closely to the predicted exponential pattern. Changes in the slopes of the continuous graphic recordings were especially noted at points at which the meter factor had been changed. On the basis of the average constant of decrement and the half times of the two curves,[1, 20] approximately 44 per cent of the circulatory volume was being exchanged per minute. In order to determine plasma and cell volume, the syringe which contained radioactive albumin had been measured previously with a scintillation detector, and another syringe of the same size which contained a solution of approximately 30 μc of I^{131} sodium iodide was also counted in an identical position. Residual radiation from each syringe was also counted after injection. At 12 minutes after injection, a sample of venous blood in "double oxalate" was obtained for determination of plasma and whole blood volumes. By the usual dilution formula and the ratio of net delivered dose to standard activities these volumes were ascertained by measuring radioactivity in 0.5 ml. each of plasma, of whole blood, and of diluted standard. The calculated total blood volume, plasma volume, and red cell mass of both twins were 702 ml., 476 ml., and 226 ml., respectively. On the basis of the calculated per cent of circulatory volume exchanged per minute and the calculated total blood volume, approximately 300 ml. of blood was being transferred per minute between the twins, or 150 ml. per minute from one twin to the other. After the samples of blood for determination of volume were withdrawn, the scintillation counter was moved along both sides of the bridge to determine whether there were large vascular shunts or areas of pooling. No localized concentration of I^{131} activity was detected. There was some slight increase in activity over the center of the bridge, expected on the basis of a greater amount of tissue.

The dose of radioactive material may be of interest. With 30 μc, high counts were recorded over the twins' heads, indicating that 5 μc would have been sufficient. Scintillation counters with larger crystals would have permitted even lower activity. To preclude any concentration of I^{131} in the thyroids, both twins were given doses of iodides before, and for some time after, the isotope determinations. In addition, both twins had received iodine-containing contrast media during their earlier x-ray studies.

Electroencephalographic studies (Dr. Rudolf C. Engel). An electroencephalogram was taken on Aug. 14, 1959, with the use of eight channels of a Grass machine. Disc electrodes were placed with collodion over the frontal, parietal, occipital, and temporal areas on both sides of each baby's head. Tracings were taken intermittently over a 4-hour period, recording both right, both left hemispheres, or right and left hemispheres of the same baby.

At the beginning of the recording both babies were quiet. No dominant occipital frequency was found in either case. In D.'s tracing the frequency varied from 2 to 15 cycles per second with an amplitude up to 160 microvolts. She seemed to become drowsy at that time. At the same time, J.'s tracing pulsated at a different rate with an activity of from 5 to 15 cycles per second, interrupted only rarely by 2 per second slow waves with an amplitude of 100 microvolts. When J. became sleepy, the number of slow waves also increased and 2 per second waves followed by rudimentary sleep spindles occurred. Beta frequencies superimposed on the slow waves in the frontal leads were seen in both cases.

Photic stimulation was followed by an upward deflection of about 50 microvolts in J.'s right occipital area, with a latency of 127 milliseconds, but no consistent response was seen in D.'s tracing.

Acoustic stimulation by clapping of the hands was followed by a marked alteration of the pattern described as the K-complex in the case of D., whereas J. showed no significant response. The EEG was repeated

on both twins on October 2, with the use of an eight-channel Offner transistor EEG machine. Neither twin showed a dominant occipital frequency. The activity varied in both cases from 2 to 10 cycles per second, with faster activity superimposed, mostly over the frontal leads. The amplitude in both cases reached 150 microvolts. Well-developed sleep spindles, 12 to 15 cycles per second, occurred first in J. and later on in D. Photic stimulation failed to evoke an interpretable response in the occipital areas in either twin. Clapping of the hands altered the pattern only in D.'s tracing. When the general pattern during sleep and wakefulness was compared between the twins, there was about the same similarity between the left and right hemisphere in the same individual, but the different stages occurred at different times. If both twins were asleep at the same time, the sleep pattern in general was the same, but there was no synchrony in sleep spindles.

Tracings taken on the first postoperative day were considerably different. J.'s tracing showed a marked depression of activity below the previously observed range of frequency, affecting the right hemisphere more than the left. Sharp waves and spikes were not recorded. D.'s tracings taken during sleep showed well-developed sleep spindles and no significant difference between the two sides.

Blood group studies (Dr. Martha L. Hamilton). The first step taken in obtaining blood for the operation on the conjoined twins was to establish as many of the blood antigens as possible. By this time, the vascular connection was known to be great, and the bloods, if not identical, were compatible. In 1953, a human blood-group chimera was reported in the *British Medical Journal*.[21] Since then, other examples of blood chimerism have been reported.[22-26] All of these were mixtures of "O" and "A" cells. When the blood of the twins was found to be group O, the possibility of a mixture group of O and A cells was considered. We felt that if A antigen were present in these infants, it most likely would be difficult to demonstrate.

The grouping procedure was repeated at 4° C., and was done by adding Coombs serum in the same manner as a D^u determination. No A antigen was demonstrated. A reverse typing was done, but the expected isoagglutinins were not observed. This is not an uncommon finding in this age group, because the titers in the serum are often low. When an indirect Coombs test was added, however, aggutination of the known A and B cells was seen. Other results are listed in the summary table.

Three units (1,500 ml.) was felt to be sufficient for transfusion needs. Additional blood was to be available so that the oxygenator pump of the open-heart operation unit could be used if needed; two walking donors were to be alerted prior to operation. Ethylenediaminetetra-acetic acid (EDTA)

Table II. Blood typing

Type	*Joined twins Sept. 2*	*D. Dec. 3*	*J. Dec. 3*	*Father Dec. 14*	*Mother Dec. 14*
ABO	0	0	0	0	0
C	+	+	+	+	Neg.
D	+	+	+	+	+
E	Neg.	Neg.	Neg.	Neg.	Neg.
c	+	+	+	Neg.	+
e	+	+	+	+	+
Kell	Neg.	Neg.	Neg.	Neg.	Neg.
M	+	+	+	+	+
N	+*	Neg.	Neg.	Neg.	Neg.
Duffy		Neg.	Neg.	Neg.	Neg.
Probable genotype		CDe/cde	CDe/cde	CDe/CDe	cDe/cde

*This result is felt to be a technical error. This typing was done by the slide method. Other N typing was done by a test tube method.

was chosen for the transfusion, and heparinized blood was obtained for the pump. Blood was secured from the American Red Cross with a special drawing the evening before operation (Table II).

The infants' blood groups were again assayed 2 months after separation. The noteworthy similarity is indicated in Table II. The relative chance of dizygosity is only 0.0187.[26]

INTERPRETATION OF PREOPERATIVE STUDIES

The lack of clinical, electrocardiographic, and radiologic evidence of serious cardiac anomalies suggested that, if present, cardiac abnormality was minor and probably would not increase the risk of operation. There was, however, considerable doubt concerning the course of venous drainage from the united livers to the hearts. It was anticipated that splenoportal venography might have to be undertaken during the process of separation, and that a venous graft might be required in the event of anomalous venous return to the hearts. Accordingly, a supply of blood vessel grafts, mechanical bypass equipment, and a cardiac surgeon were to be available on a stand-by basis. Pyelography had suggested that in all probability the aortas and abdominal inferior vena cavas were normal. Cholecystography had led us to believe that the external biliary systems were separate. It also seemed certain that there was no intraluminal communication between the intestinal tracts, such as might occur in the region of the omphalomesenteric duct.[9]

The intertwin shunt of blood, however, seemed rather large. Whether the shunt was confined to intrahepatic sinusoidal anastomosis and to smaller vessels of skin and muscle in the bridge, or whether some large vessel was shared was not certain. The delay in intertwin mixing encountered in pyelography and in isotopic transfer was not sufficient to provide a clear conclusion. Certainly a shunt which could siphon more than 20 per cent of the cardiac output of each was a worrisome fact.

Dr. Ian Aird was kind enough to visit the twins and to assay the problem. His opinion was that the bridge was at the extreme upper limit of operability; fortunately, he concurred with our decision to delay separation.

The size of the shunt made determination of zygosity based upon blood antigens inconclusive; these would have to wait upon separation of the two blood streams. Also, the speed of intermingling dissipated any attempts to determine adrenal function in the individual infants. This would have been highly desirable because of Aird's[1] discovery of adrenal anomaly in one of his twins. Electroencephalographic studies suggested that neither twin had a serious cerebral defect.

The planning conferences included all those who had roles in care, diagnosis, operative techniques, and postoperative management. Some of the smooth teamwork can be ascribed to these meetings.

SURGICAL SEPARATION (OCT. 6, 1959)

Because of the previously mentioned abnormality of the adrenals in one of Aird's twins, it was elected to provide adrenal support before, during, and after the operation. ACTH gel was injected intramuscularly in each twin in a dose of 5 mg. at preoperative times of 24, 12, and 0 hours, and then daily through the fourth postoperative day. In addition, 5 mg. of hydrocortisone was administered intravenously to each twin at the beginning of the operation and at the rate of 1 mg. per hour for the duration of anesthesia. Thereafter, for the remainder of the day, hydrocortisone was given intravenously at the rate of 0.5 mg. per hour.

On the second postoperative day, 5 mg. of hydrocortisone was injected intramuscularly every 8 hours, 2.5 mg. every 8 hours on the third postoperative day, and on the fourth day none was given. The postoperative behavior of the twins indicated that their adrenal function was normal. Atropine sulfate, 0.1 mg., was given subcutaneously

to each twin 2 hours before operation, and all oral food and liquid were withheld beginning 6 hours before operation. Their preoperative fluid and electrolyte requirements were adjusted with a glucose-sodium-potassium solution, and they were maintained during operation on a solution of 5 per cent glucose in distilled water.

Anesthetic agents were administered endotracheally. There was considerable difficulty encountered in intubation because of the necessity of maintaining the lateral decubitus position. The primary agent was nitrous oxide and oxygen, and ether, cyclopropane, and succinylcholine were the secondary agents. Insertion of the intravenous catheters and draping were accomplished before anesthesia was begun. In spite of this the total anesthetic time was 5½ hours.

The technical details of the operation are described elsewhere.[27] The major problems were the division of the hepatic bridge and the closure of the formidable thoracoabdominal defect. The liver bridge measured 4.5 by 13 cm. Portal and hepatic veins were in normal positions. The umbilical vessels diverged to enter their respective livers only a few centimeters before they entered the hepatic parenchyma. Bleeding was controlled by pressure and by ligation of the larger vessels. There were two pericardial cavities, but the opposing pericardial surfaces were joined in a common septum. The latter was given to J., and the resulting defect in D.'s sac was closed without difficulty. The defect in the two hepatic surfaces was closed by approximation of the hepatic capsules, and a rubber drain was brought to the skin surface through a separate incision. Loss of blood up to this point was only about 100 c.c. It was now necessary to tunnel extensively under the skin in order to mobilize the latter to close the anterior defect in each twin. To achieve this end, it was also necessary to add rather large relaxing incisions bilaterally in each twin's flank. The major part of the loss of blood shared between the twins occurred during the process of skin mobilization. About one fourth of the total 4½ hours of operation time was devoted to the closure of the abdominal defects. The twins had smooth operative and immediately postoperative periods and seemed to withstand the procedure remarkably well.

When there are no other complicating anomalies, it seems likely that the limiting factor in separation of thoracopagus twins is the size of the thoracoabdominal defect. Although no necrosis of the skin flaps occurred, it seems likely that, had the twins been any older, the extensive separation of the skin either could not have been accomplished at operation or would have been followed by calamitous sloughing.

POSTOPERATIVE COURSE

J.'s loss of blood was 280 ml., of which 271 ml. was replaced during the operation, and an additional 65 ml. was given during the first 4 postoperative hours. D.'s loss during the separation was 325 ml.; she was given 350 ml. during the division. D.'s relaxing incisions were larger than her sister's, so that during the first 4 postoperative hours she was transfused with an additional 110 ml. of whole blood. Her postoperative loss was estimated as 150 ml., and J.'s, 100 ml. Twelve hours after operation the oozing of blood and plasma from the relaxing incisions had largely ceased. The hemoglobin level of each twin was at its preoperative level (11.4 to 11.8 Gm. per 100 ml.) a week after separation, and never fell below 9 Gm. during the immediate postoperative period.

For the first 10 hours after separation the clinical courses were relatively uneventful. Temperature, pulse, and respiration stabilized rapidly. The twins' color and behavior remained good. At the eleventh hour, however, J. suddenly developed labored respiration, pallor, cyanosis, and increased muscle tone, and her eyes rolled upward. This episode lasted 10 minutes. Two hours later it was repeated, this time initiated by twitching of the hands, and left-sided clonic movements. This seizure lasted 30 minutes. A total of ten convulsions occurred from the eleventh to the nineteenth hour after

operation. The majority were left sided, associated with twitching of the muscles of the eyes and face, occasionally with sucking movements, opisthotonus, and rigidity of the extremities. Only once was a seizure right sided. Three milliliters of 10 per cent calcium gluconate was injected intravenously without effect. This was followed by 12.5 mg. of sodium diphenylhydantoin (Dilantin) administered intravenously in amounts of 7 mg. every 8 hours (5 mg. per kilogram per 24 hours). During the same period D. had two seizures, at 14 and 16 hours after operation. Like J.'s, her manifestations were also predominantly left sided, with cyanosis of the hands and feet and a decrease in the temperature of the skin. In neither twin was there a definite response to intravenous calcium gluconate, but Dilantin did control the attacks. After 48 hours, administration of Dilantin to D. was discontinued, but it was given to J. for 28 days. Postoperative electroencephalograms, behavioral development, environmental responses, and neurological examinations have all been normal to date. There have been no further seizures.

Two hours postoperatively it was noted that the secretions aspirated from the twins' throats had thickened. By the fifth hour, J., and, by the seventh, D. had manifested grunting respirations, although their respiratory rates had not increased. Shortly thereafter, coarse rhonchi appeared in both twins' lung fields. Respiratory difficulty increased in both, so that by 15 hours postoperatively, bronchial obstruction was manifest by shifting areas of emphysema or atelectasis. By the seventeenth hour, J.'s difficulty had progressed to such an extent that tracheostomy was required to provide an avenue for easier access to the bronchial secretions. D., however, did not reach a critical respiratory state, and by the second postoperative day her respiratory difficulty was improving and had largely subsided by the end of the first week. At the peak of D.'s

Fig. 3. Separated twins at 5½ months of age (J. in front).

Table III. Immediate postoperative balance—J.

October 1959	*Route*	*Input per day*					*Route*	*Output*		
		Calories	*Volume (ml.)*	*Na (mEq.)*	*K (mEq.)*	*Cl (mEq.)*		*Volume (ml.)*	*Na (mEq.)*	*K (mEq.)*
6	I.V.	110	540	9	6	6	Urine	105		
							Gastric	55	15	1
7	I.V.	116	580	19	8	28	Urine	141	3	9
							Gastric	90	10	1
8	I.V.	140	710	16	14	29	Urine	460	6	8
							Gastric	70	4	1
9	I.V.	106	530	16	3	13	Urine	630	1	10
							Gastric	94	4	1
10	I.V.	300	720	7	4	10	Urine	450	1	2
11	I.V.	220	550	9	5	7	Urine	860	< 1	3
	Oral	160	365	3	7					
12	I.V.	60	310	8		7	Urine	708	< 1	3
	Oral	480	730	11	21					
13	I.V.	40	210				Urine	780	3	2
	Oral	650	975	14	28					
14										
	Oral	650	980	13	26		Urine	552	2	8
15	I.V.	80	390				Urine	664	9	8
	Oral	665	1,000	26	30	3				
16	I.V.	60	305				Urine	680	14	10
	Oral	600	970	26	30	3				
17	I.V.	50	240				Urine	712	16	7
	Oral	580	896	23	27	3				
18	I.V.	30	145				Urine	680	1	6
	Oral	520	820	21	24	2				
19							Urine	550	6	8
	Oral	665	1,006	26	30	3				

*S, steroid therapy; F, febrile; C, convulsions; E, edema; R, respiratory difficulty; U, diuresis; D, diarrhea.

†R = tracheostomy.

‡R = serum bicarb. 26 mEq. per liter, pH 7.12, pCO_2 80 mm. Hg.

respiratory problem a small pneumothorax appeared over the right upper lobe, but this disappeared without further expansion. J., on the other hand, had increasing difficulty through the fourth postoperative day. Her secretions became thicker and thicker, until their consistency was rubbery. Consequently, ever-deeper tracheal suction was required in order to provide an adequate airway. By auscultation it was possible to ascertain the obstructed lobe, determine when the suction tip had reached to the bronchial orifice of this lobe, and to hear when the bronchial plug was removed and the lobe was again ventilating. In spite of the latter manipulations, intratracheal instillation of 3 per cent sodium bicarbonate solution and of Isuprel, and maintenance of an atmosphere of high humidity, the bronchi were increasingly difficult to evacuate. The obstructing plugs resembled 1 by 3 mm. leather casts of the major bronchi. By the fourth day her status had declined to such an extent that she was kept free of cyanosis only by 100 per cent oxygen delivered by positive pressure directly into the tracheostomy tube, and finally was kept alive only by artificial respiration maintained by hand-manipulated bag-breathing.

per day		Measured balance per day					Serum levels (mEq./L.)		
K (mEq.)	Cl (mEq.)	HOH (c.c.)	Na (mEq.)	K (mEq.)	Cl (mEq.)	Status*	Na	K	Cl
		+380				S			
1	18								
9		+249	+ 6	− 2		SFCR†	126	6	
1	12						136	6	
8		+180	+ 6	+ 4		SFCR			
1	8								
10	2	−194	+11	− 8	+ 2	SFER	141	7	
1	9						136	8	
2	1	+270	+ 6	+ 2	+ 9	SF R‡	119	4	103
3	2	+ 55	+10	+ 9	+ 5	SFUR	129	5	102
3		+322	+18	+19	+ 7	FUR§			
2		+405	+11	+26		DFR			
		+428	+11	+18		DFR			
8	9								
8	17	+526	+17	+22	−14	DF			
10	3	+595	+12	+20		DF			
7	4	+424	+ 7	+20		DF			
6	2	+285	+20	+18		DF			
8	9	+456	+20	+22		DF¶			

‡Body weight, 4.77 kilograms.
¶Body weight, 5.11 kilograms.

Various mechanical devices designed as respirators were tried without success. At the depth of her difficulty, J. was in serious ventilatory distress; the arterial bicarbonate was 26 mEq. per liter, pH 7.12, and the calculated arterial serum carbon-dioxide tension was 80 mm. Hg. Bag-breathing was maintained by hand for the next 12 hours and intermittently for 12 more. By the end of the fifth postoperative day most of the leathery casts had been aspirated and the bronchial secretions were noted to be more liquid in consistency. Also, the episodes of bronchospasm, somewhat relieved by Isuprel intratracheally and by epinephrine subcutaneously, were becoming less frequent and less severe. Assisted respiratory effort was no longer required and the level of inspired oxygen was rapidly dropped to 40 per cent. By the eighth postoperative day J.'s now thin secretions could be aspirated satisfactorily at the end of the tracheostomy tube, and at the end of the second week the respiratory difficulty had largely subsided.

During the initial 24 hours after separation, J.'s temperature did not exceed 99.6° F. rectally, whereas D.'s reached 100.4°. For the ensuing 15 days J.'s temperature

ranged from 97° to 102.8° F.; the most frequent irregularity was from 100° to 102°. D.'s irregularity was somewhat more limited in range, from 99° to 101.6°, and disappeared on the ninth postoperative day. Their white blood cell counts shifted from a preoperative level of 7,000 to 8,000 to about 14,000 cells per cubic millimeter at the end of the first week. There was a corresponding shift in the neutrophil distribution, from 30 to 60 per cent.

D., on the fifth day, and J., on the seventh day, developed watery diarrhea; there were as many as twenty stools per day; the total duration of the diarrhea was 6 to 8 days. At no time was there any interference with appetite. The twins' oral intake was supplemented as needed by intravenous fluids, and their formula was changed temporarily to a high-protein, low-fat mixture.

On the fifth postoperative day, D.'s buttocks were noted to be erythematous, hot, tense, tender, and deeply indurated. Although the sites of antibiotic injections had been rotated between the anterior thighs and buttocks, apparently the injections into the latter had not been given deeply enough. The gluteal inflammation progressed to mild central softening and then began to subside on the eighth day. Incision and drainage were not required.

Although the mobilized skin in each twin had been secured with stay sutures, on the ninth day after operation the edges of D.'s relaxing incisions were noted to slip loosely over the underlying tissue, at times exposing underlying liver and bowel. The edges were promptly secured with interrupted sutures. On the twelfth day a similar event occurred in J.'s incisions, and this was managed similarly. Three days later J.'s midline incision showed a few small areas of superficial necrosis. On the fifteenth day the exposed surfaces of the relaxing wounds in each twin appeared a light green. This superficial infection was satisfactorily treated with 1 per cent acetic acid packs. After this episode had subsided, D.'s relaxing wounds were covered with skin homografts on the twenty-first day. The left homograft succumbed promptly, but that on the right was rejected 13 days after application. In each twin, epithelialization was sufficiently vigorous that isografts were not required. The granulating surfaces were covered within 2 months of operation.

Cultures of bronchial secretions, diarrheal stools, relaxing wounds, and nasopharynx

Table IV. Immediate postoperative balance—D.

		Input per day						*Outp*		*per day*	
October 1959	*Route*	*Calories*	*Volume (ml.)*	*Na (mEq.)*	*K (mEq.)*	*Cl (mEq.)*	*Route*	*Volume (ml.)*	*Na (mEq.)*	*K (mEq.)*	
6	I.V.	110	540	9	6	6	Urine	123			
							Gastric	75			
7	I.V.	110	550	18	7	24	Urine	450	< 1	11	
							Gastric	110	10	< 1	
8	I.V.	180	650	20	12	24	Urine	340	< 1	6	
	Oral	160	250	4	7		Gastric	282	25	6	
9	I.V.	75	350	9	7	9	Urine	700	< 1	11	
	Oral	360	805	6	13						
10	I.V.	10	55				Urine	480	< 1	11	
	Oral	540	815	11	18						
11											
	Oral	500	755	11	18		Urine	372	1	11	
12	I.V.	50	250	5		4	Urine	540	< 1	8	
	Oral	540	810	13	20						

*S, steroid; F, fever; D, diarrhea; R, respiratory difficulty; A, gluteal cellulitis; C, convulsion.

†Body weight, 4.15 kilograms.

from the twins consistently grew *Pseudomonas aeruginosa*. This organism had been present in the nasopharynx of each twin from the age of 1 month. Immediately after separation, penicillin and erythromycin had been started intravenously in both twins. The Pseudomonas organism was sensitive to a wide range of antibiotics, and as soon as the organism was discovered in the bronchial secretions, tetracycline was substituted for the penicillin and erythromycin. Although none of the antibiotics eliminated the Pseudomonas, there was no extensive infection such as pneumonia or peritonitis. Removal of the sutures from the central incision was begun on the twentieth day, without incident.

The plan of corticosteroid support as described in the operative note was followed for D.; J.'s therapy was continued for 2 additional days, because of the distressful complications in her postoperative course. The possibility that J. might have been the parasitic twin was suggested by D.'s vigor and by her somewhat superior growth.

Immediately prior to separation the twins' combined weight was 8.55 kilograms, their length was 54.5 cm., and their estimated surface area[28] was 0.26 sq. M. Their estimated water requirement per day was from 600 to 800 ml., their estimated sodium requirement was from 22 to 26 mEq. per day, and their potassium requirement was from 16 to 20 mEq. Their anticipated urine output was from 150 to 250 ml. per day, and their insensible loss was from 200 to 300 ml. per day. For the day of separation it was planned to keep water and sodium intake at levels about half of the estimated requirements but to give full potassium intake once the infants began to void. Calories were supplied during the first few postoperative days by the addition of glucose (5 per cent) and ethanol (1 per cent) to the intravenous fluids. By the fourth day, 10 per cent glucose was substituted for 5 per cent glucose and 1 per cent ethanol. Milk was begun on the second postoperative day for D. and on the fifth postoperative day for J. Because of her tracheostomy, J. was fed by nasogastric tube, whereas D. was allowed to suckle. Gastric suction was maintained through the third postoperative day, and its volume as well as sodium, potassium, and chloride contents were measured daily. The volume of urinary output was measured hourly, and its sodium, potassium, and chloride output, daily. These measurements

Outp	per day		Measured balance per day					Serum levels (mEq./L.)		
Na (mEq.)	K (mEq.)	Cl (mEq.)	HOH (c.c.)	Na (mEq.)	K (mEq.)	Cl (mEq.)	Status*	Na	K	Cl
			+342				S			
<1	11		− 10	+ 7	− 5		SFCR	122	6	
10	<1	11						135	6	
<1	6		+278	− 2	+ 7		SFR			
25	6	50								
<1	11	1	+455	+14	+ 9	+8	SFR	134	6	
<1	11	<1	+390	+10	+ 7		FR	127	5	97
			+383	+10	+ 7		FDRA			
1	11	1								
<1	8	1	+520	+17	+12	+3	FDRA†			

are given in Tables III and IV. Information on the oliguria which occurred during J.'s periods of severe hypoxia is not given in the tables. During episodes of apnea and cyanosis, especially during the time when artificial respiration was required, her urinary output would cease. Then, as she began to breathe unassisted, the urine volume would increase to 5 to 10 ml. per hour. After the acute respiratory embarrassment had subsided, she could excrete easily from 10 to 40 ml. per hour.

PRESENT STATUS

Aside from the complications noted in the postoperative course, D.'s progress was essentially asymptomatic. From November 3 to 7, she had a mild mucoid rhinitis, and from December 8 to 15, mild afebrile diarrhea. She was discharged home on December 16. Subsequent heights and weights are shown in Table I.

The chief problem of J.'s postoperative course was essentially the removal of the tracheostomy tube, which was not accomplished until Jan. 16, 1960. By January 22 the nasogastric tube was removed and she was placed on oral feedings. During this period her weight dropped from 6.7 to 6.2 kilograms. By February 12, however, she was gaining weight well; she had a good response to her environment, and she was discharged home on February 17.

During the early part of December, it was noted that her gain in height was poor, in spite of progressive gaining of weight. Extensive evaluation of her status, including duodenal aspiration for trypsin and serum butyl extractable iodides and protein-bound iodides, disclosed no reason for the poor gain in height. Toward the latter part of December, however, concerted attempts were made to correct her lordosis during measurement, and by this means her measurements were at more appropriate values.

During the 4½ months' postoperative period she had frequent stools which were softer than normal but did not contain pus or pathologic organisms. Otherwise, her postoperative course was complicated only by her respiratory difficulties.

Late in the postoperative period, fluoroscopic examination of the chest demonstrated a dextroposition of the heart, which was confirmed by electrocardiography. The heart, however, was normal in contour, rotation, and pulsation.

J.'s height and weight at various times are shown in Table I.

After having been home for 7 weeks, on March 26, 1960, J. developed fever and tachypnea. Because management on antibiotics seemed to produce no relief, she was readmitted to the University Hospital on April 5, 1960. Extensive pneumonia was demonstrated, from which pneumococci were cultured. In addition, it was noted that her chest development was poor. All of her respiration was diaphragmatic. Although her temperature and white blood cell count responded satisfactorily to penicillin and Terramycin, the respiratory difficulty increased and she died on April 9. The significant findings at autopsy were extensive bilateral pneumonia and virtually nonexistent sternocostal junctions. The latter anomaly apparently was responsible for the poor chest development and possibly for the development of pneumonia.

D. was examined again at the University Hospital on June 20, 1960. Her psychomotor performance was approaching the 1-year level. Her weight was 7.74 kilograms and her height was 64.5 cm. She had had several respiratory infections since discharge but none was serious. In contrast to her sister's chest, D.'s was apparently developing normally. In spite of abdominal binders, the abdomen was still markedly protuberant. Chest circumference was 44.5 cm.; maximum abdominal circumference was 46.75 cm.

D. still has another formidable obstacle to overcome: support of the anterior abdominal wall. At separation the remnants of abdominal musculature and fascia were so widely separated that no approximation could be accomplished. Whether isografting or the use of an artificial prosthesis is the procedure of choice remains to be decided.

SUMMARY

Thoracoabdominally conjoined twins were studied from shortly after birth, through surgical separation, to successful discharge. Certain special observations are reported in some detail. The postoperative course was complicated by extensive tracheobronchial infection, from which recovery was complete.

The authors gratefully acknowledge the invaluable assistance of Mrs. Maxine Allen.

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Bulging fontanel: a complication of tetracycline therapy in infants

John P. Fields, M.D.*

NASHVILLE, TENN.

BY FAR the most frequent untoward side effect of therapy with the tetracyclines is gastroenteritis. Skin rashes, angioneurotic edema, and anaphylaxis are well recognized but rare complications, and benign intracranial hypertension manifested in infants by bulging of the fontanel occurs occasionally.

Bulging of the anterior fontanel has serious implications, and creates a problem in differential diagnosis, since the patients receiving tetracycline therapy are usually ill. Therefore, it is felt that the relationship of a bulging fontanel o tetracycline therapy should be reported, to call attention to it as a cause of intracranial hypertension and to aid the practitioner in better evaluating its significance.

Tetracycline-induced increased intracranial pressure appears to be well known in this locality, although only two brief references[1, 2] to it have been found in the literature. Members of the Vanderbilt Pediatric Staff have frequently commented on this complication, and several patients have been hospitalized for its evaluation and others have been followed on an outpatient basis.

The following cases have recently been seen on the Pediatric Service at Vanderbilt University Hospital.

CASE REPORTS

J. K., a 4-month-old white male, was in previous good health until 36 hours prior to admission when he developed cough and fever with decrease in appetite. He was seen by a physician and a diagnosis of bronchitis was made. Tetracycline phosphate complex was started at a dose of 50 mg. every 6 hours. The anterior fontanel was examined at this time and was normal. Twelve hours later the baby vomited and was thought to be rather irritable. Shortly thereafter the fontanel was noted to be "sticking up" and the patient was admitted to Vanderbilt University Hospital. The tetracycline had been given four times in the dosage prescribed.

On admission to the hospital the patient was lethargic. The temperature, pulse, and respirations were normal. The head was 42 cm. in circumference. The anterior fontanel was bulging and tense; it did not vary with changes in position. The posterior fontanel was closed. The eyes were normal, with flat optic discs. The ears and mouth were

From the Department of Pediatrics, Vanderbilt University School of Medicine and Vanderbilt University Hospital.

**Address, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville 5, Tenn.*

not remarkable. The neck was supple. The chest was clear. The remainder of the examination was completely normal.

The urine, the white blood cell count, its differential, and the hemoglobin level were normal. Lumbar puncture revealed clear cerebrospinal fluid under "increased pressure"; the infant, however, was crying and the actual pressure was not recorded. The cerebrospinal fluid protein was 20 mg. per cent, and sugar was 57 mg. per cent. There were no cells and cultures were sterile. Subdural taps were done bilaterally; no fluid was obtained. Roentgenograms of the skull revealed questionable spreading of the sutures, and the bulging fontanel was noted. Tuberculin and histoplasmin skin tests were negative.

The administration of tetracycline was discontinued, and the patient was observed for 48 hours. The tense, bulging fontanel returned to normal immediately after the lumbar puncture and tapping of the subdural spaces. The patient remained afebrile and has been followed closely since then. At 6 months of age he is doing well, developing normally, and has had no recurrence of the bulging fontanel.

M. B., a 6-month-old white female, was in good health until 4 days prior to admission when she developed cough and mild difficulty in breathing. A diagnosis of bronchiolitis was made and the patient was started on tetracycline phosphate complex which was given regularly in a dose of 50 mg. every 6 hours. The day of admission the anterior fontanel was noted to be bulging, and the patient was admitted to Vanderbilt University Hospital.

On admission she was irritable and in respiratory distress. The temperature was 101.4° F., pulse was 140, and the respiratory rate was 60. The head was normal except that the anterior fontanel was bulging and tense. The eye grounds were not remarkable. The neck was supple. There were expiratory wheezes present throughout the chest. The remainder of the physical examination was within normal limits.

The urinalysis was normal on admission. The white blood cell count ranged from 16,800 to 21,000 per cubic millimeter with a normal differential. The hemoglobin level was 13.6 Gm. per cent. Tuberculin and histoplasmin skin tests were negative. The cerebrospinal fluid was clear, containing 4 red blood cells and 1 white cell per cubic millimeter. The protein content was 24 mg. per cent, and the sugar was 59 mg. per cent. Cultures of the cerebrospinal fluid and of two blood specimens were sterile. The cerebrospinal fluid was not measured. A roentgenogram of the chest was normal; subdural taps and films of the skull were not obtained.

The administration of tetracycline was discontinued and chloramphenicol was substituted for it. The bulging of the fontanel disappeared within a few hours and did not recur. The patient's respiratory difficulty was gradually overcome, and she was discharged on the sixth hospital day completely free of any symptoms. The child has subsequently been followed for over a year and is doing well with normal development and no recurrence of any neurological symptoms.

DISCUSSION

No reports in the English literature were found, specifically dealing with benign intracranial hypertension caused by tetracycline compounds. Millichap[1] and Gellis[2] comment briefly on this problem but only to state that it does occur. In view of the widespread use of the tetracyclines it was felt that such an alarming reaction should be reported in more detail.

The relationship between tetracycline therapy and increased intracranial pressure seems to be more than coincidental. Withdrawal of the drug was associated with prompt return of the fontanel to normal in the 2 patients cited here. They were not receiving any other medication. Subdural hematoma and meningitis, the more common causes of bulging fontanel, were not present in either patient. Among the more unusual causes of intracranial hypertension are lack or excess of vitamin A and

hypophosphatasia, neither of which would seem to play a role here. Otitic hydrocephalus was not considered because of the lack of otitis media and the short benign course of the reaction. Dees and McKay[3] report 3 cases of older asthmatic children with benign intracranial hypertension which developed during treatment with adrenal steroids. Hypochromic, microcytic anemia has been reported as a cause of increased intracranial pressure but occurs primarily in adolescent females.[4] Anemia is not reported as a cause of intracranial hypertension in infancy. The mechanism of this reaction is not clear. We have observed no relationship between the dose or length of therapy and the production of the bulging fontanel.

Careful evaluation of patients with a bulging fontanel should be carried out and other causes investigated before a diagnosis of a reaction to tetracycline is made.

SUMMARY

Tetracycline compounds can be a cause of increased intracranial pressure as manifested by bulging of the fontanel. This benign but alarming reaction disappears on withdrawal of the drug.

I am indebted to Dr. Luther Beazley for the opportunity to report the second case.

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Accidental isolated primary vaccinia of the tongue

Edwin P. Scott, M.D., and Alex J. Steigman, M.D.*

LOUISVILLE, KY.

THE condition to be described and documented appears to be rare despite the frequent opportunities which occur for the introduction of vaccinia virus onto the tongue of normally active children. Accidental autoinoculation of vaccinia to other parts of the body is not particularly rare.

Curth, Curth, and Gard[1] reviewed the complications of mass vaccination in New York City in 1947 and enumerated no instances of lingual vaccinia. Standard American clinical and virologic textbooks consulted make no reference to such an occurrence.[2, 3]

In order to document an isolated lingual lesion as primary vaccinia, the following criteria should be met:

1. A susceptible individual with an opportunity for inoculation of living vaccinia virus onto the tongue.
2. Appearance of a lesion consistent with the proliferation and necrosis which characterize primary vaccinia.
3. A rising antibody titer to vaccinia virus in the patient.
4. Demonstration of histologic changes consistent with primary vaccinia.
5. Upon resolution of the lingual lesion, inability to successfully establish primary vaccination in the subject when inoculated with vaccine lymph of known potency.
6. Recovery of vaccinia virus from the lesion.

Except for recovery of virus, we have established all of these criteria in one case to be illustrated and described in detail in this report, and one of us (E. P. S.) has also seen a child involved in the same chain of infection as this patient in whom the clinical picture was that of isolated lingual primary vaccinia.

From The Department of Pediatrics, University of Louisville, and The Children's Hospital, Louisville.

**Address, Department of Pediatrics, University of Louisville School of Medicine, 323 East Chestnut Street, Louisville 2, Ky.*

CASE REPORT

M. H. W., white female aged 4½ months, entered Children's Hospital on June 6, 1959; the mother's chief complaint proved to be the correct diagnosis, namely, "vaccination of the tongue."

The relevant chain of events is as follows: Sibling A, aged 5 years, was vaccinated on May 13, 1959. On or about May 20 the dressing and lesion were disturbed by a neighbor's child; soon afterward sibling B, aged 16 months, a habitual biter, bit sibling A on the vaccination site. Some days afterward (not attended by a physician and the details are not precise) B developed a sore on the tongue and fever for 2 days and seemed quite ill; the mother, unfamiliar with

the rarity of the lesion, diagnosed this as "vaccination of the tongue" and painted it with gentian violet. This same sibling B, while still febrile, and toddling about, was found to have taken away the nursing bottle of M. H. W., aged 4½ months (the case to be described in greater detail), sucked on it, and in a fit of rage forced it back into the mouth of M. H. W.; this event transpired either 7 or 8 days prior to hospital admission.

M. H. W., the hospitalized patient, had fever, vomiting, and diarrhea for 3 days prior to admission on June 6, 1959, when examination revealed a well-developed, slightly dehydrated infant with a large indurated ulcer approximately 3 cm. in diameter on the mid-dorsum of the tongue (Fig. 1). The edges were slightly raised, the center depressed and the edges rather firm to the examining finger; sublingual and submaxillary nodes were palpable. Within 3 days of admission the infant was able to suck without pain and the lesion had begun to involute; when seen 9 days after admission, the ulcerated lesion of the tongue was clearly visible but now smaller, measuring approximately 1 cm. by 0.75 cm. It was at this time that sibling B's tongue was first seen by a physician (E. P. S.) and found to have a depressed, well-healed scar on the dorsum. M. H. W. was rephotographed Nov. 11, 1959 (Fig. 2) and found to have a depressed scar at the site of the original lesion noticed in June.

Fig. 1. Appearance of tongue 11 days following traumatic inoculation of vaccinia virus. The edges are slightly raised and firm to the touch, the center slightly depressed.

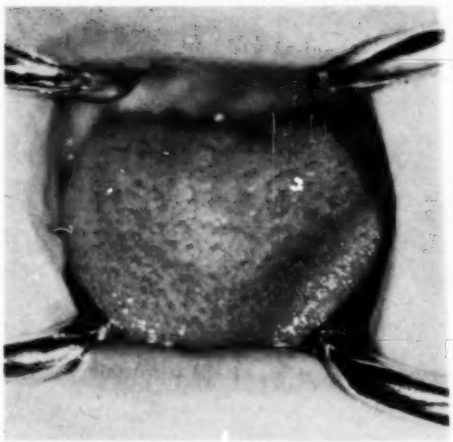

Fig. 2. Appearance of tongue 5 months after primary lesion. Well-healed slightly depressed scar.

Laboratory and revaccination data. There were 12 Gm. of hemoglobin per 100 ml. of blood and the peripheral white blood count revealed 7,800 cells of which 35 per cent were polymorphonuclear leukocytes, and 65 per cent were lymphocytes. Blood serum was collected for special virus studies. Scrapings of the tongue ulcer "showed numerous squamous epithelial cells and abundant pus cells. Rare epithelial cells present cytoplasmic eosinophilic or amphophilic inclusion bodies consistent with Guarnieri bodies."* Scrapings taken 4 days later and inoculated on the chorioallantoic membrane of eggs revealed no virus.†

When rephotographed (Fig. 2) Nov. 11, 1959, serum collected and contrasted with a blood serum of June 4 for vaccinia antibody revealed a rise in hemagglutination inhibition titer from 1:10 to 1:160.‡ It was not surprising therefore that, when vaccination was attempted (Nov. 11, 1959) in the left upper arm from a capillary of vaccine

*I. Diamond, Pathologist, Children's Hospital.

†E. Kotcher, Virus Diagnostic Unit, Kentucky State Department of Health.

‡C. Moscovici, University of Colorado Medical Center.

lymph which was simultaneously successfully inoculated into an unvaccinated control infant, it failed to produce vaccinia.

DISCUSSION

There appears to be little doubt that M. H. W. was accidentally but successfully vaccinated on the tongue as the result of introduction of vaccinia virus from the tongue of sibling B, perhaps associated with the trauma of forcing the virus-contaminated nursing bottle into her mouth. All of the criteria mentioned in the introduction were established save for recovery of the virus from scrapings taken approximately 16 days after the accidental traumatic introduction of virus. The appearance of the scarred tongue of infant sibling B who perpetrated the foul deed was consistent with a healed vaccination scar but special studies were not possible in that instance. Dr. Joseph Stokes, Jr.,[4] has referred to an instance similar to the case sibling B, in an 18-month-old infant diagnosed on clinical grounds.

One may speculate concerning the infrequency of accidental mucosal lesions in vaccinia when one considers the activities of normal children who have been vaccinated. We have seen accidental vaccinia around the conjunctiva and spreading onto the lower lid, just inside the nares involving the nasal mucocutaneous junction, and in similar situations around the vermilion border of the lip and the genitals of male and female children, but without established stomatitis, conjunctivitis, or vaginitis in our own experience. Cutaneous accidental autoinoculation has on the other hand not been rare in our experience. The stratified squamous epithelium of the tongue is not easily injured normally, but perhaps in this 4½-month-old infant traumatized by the forcible thrust of a rubber-nippled nursing bottle, damage did take place; in the 16-month-old infant, sibling B, in whom clinical isolated lingual primary vaccinia occurred, there is no antecedent history of trauma or of stomatitis; that child was a habitual biter and may have had occult trauma. One may speculate that, having become established as a lingually adapted strain in infant J. L., the virus was more easily transferred to the subject described in detail here. One may speculate why there have not been instances of accidental oral vaccinia observed in infants with lesions of primary herpetic gingivostomatitis living in crowded households with other children who have been recently vaccinated.

Finally, one may speculate concerning the age in the future at which the subject of our communication can ever be successfully vaccinated if at all. The present position of her vaccination scar is accessible to inspection but may not be as acceptable to school health inspectors and others as a scar in a more orthodox deltoid location.

SUMMARY

Two infants with vaccinia of the tongue have been described and illustrations shown; in one of them detailed criteria for this rare condition have been met and in the other one the same chain of infection can be inferred.

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Maple syrup urine disease

Margaret R. Lane, M.D.*

NEW ORLEANS, LA.

THE condition now known as "maple syrup urine disease" was first described in 1954 by Menkes, Hurst, and Craig,[1] occurring in 4 siblings. Since that time there have been 2 more cases reported and several others mentioned in the British and American literature.[2, 3] A patient reported by Smith and Strang[4] has been considered by some[6] to have had this disease and by others[2c, 3] to have had another, possibly related, condition. Subsequent reports have dealt primarily with elucidation of the chemical nature of this disease.[2, 3, 5, 6, 7]

CASE REPORT

E. G., a 4-day-old baby girl, was admitted on Aug. 6, 1959, on account of listlessness and "little convulsions" for 18 hours. She was the product of an entirely uncomplicated term third pregnancy and a normal spontaneous delivery. Birth weight was 7 pounds, 3 ounces. No abnormalities were found at birth, and the child did well for the first 2 days in the nursery.

On the third day of life, she refused her formula (1:2 evaporated milk with 5 per cent carbohydrate) and was noted to have a brief "spasm" consisting of extending her arms. From that time she nursed poorly and grew progressively more listless until the time of admission when she could be persuaded to take feedings only briefly on stimulation. There had been no vomiting, cyanosis, jaundice, or fever. The only bleeding had been a very small amount from the vagina (considered to be estrogenic effect); stools and urine had been considered to be normal. She had received no medication.

Family history revealed that a 4-year-old sibling had had seizures since 17 months of age and was retarded. Another sibling had died at 12 days of age after growing progressively worse, and autopsy had revealed only bronchopneumonia and atelectasis, cloudy swelling of the kidneys, and fatty metamorphosis of the liver. A paternal cousin died during this child's admission from a "brain hemorrhage," but no autopsy was obtained.

Physical examination. On admission the baby was very listless, holding her arms persistently in extension. She could be stimulated to cry with difficulty. Breathing was not labored but there were periods of apnea followed by periods of rapid breathing. Her color was good without jaundice or cyanosis. The head was normal in size and shape; the fontanel was not bulging or depressed. Pupils were medium sized and reacted to light. Moro reflex was absent. Muscle tonus was increased and there was no paralysis. The lungs were clear with good breath

From the Department of Pediatrics, Tulane Medical School and the Charity Hospital of Louisiana at New Orleans.

**Address, Department of Pediatrics, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans 12, La.*

sounds and no râles. The heart tones were good; rhythm and rate were normal. The abdomen was not distended, liver, spleen, and kidneys were not enlarged, and no masses were palpable.

Laboratory. The hemoglobin level was 21 Gm. per cent; white blood cells, 14,100 per cubic millimeter with 60 per cent neutrophils and 40 per cent lymphocytes. The urine was yellow and clear, with pH 6.0, no albumin, sugar, or bile. Microscopic examination was negative. Ferric chloride test was negative and the Sulkowitz reaction was strongly positive. Serologic tests for syphilis were negative. The lumbar cerebrospinal fluid was clear, not xanthochromic, under no increased pressure, and contained only 2 lymphocytes per cubic millimeter; its protein content was 30.5 mg. per cent; glucose, 102 mg. per cent; chloride, 118 mg. per cent; and routine cultures negative. Bilateral subdural taps on the third day revealed no collections of fluid. Bacterial and viral cultures from the throat, stool, and spinal fluid yielded no pathogens.

Course in the hospital. Progressive deterioration of her condition continued throughout the hospital stay. She was given oxygen and fed by gavage. She remained stuporous. Periods of extreme rigidity, with arms and legs extended and crossed, but without opisthotonus, alternated with extreme flaccidity. The latter suggested myasthenia gravis, but administration of prostigmine produced no effect.

The respirations became increasingly depressed and by the fifth day consisted of 8 to 10 deep cogwheel type gasps per minute. From the fourth hospital day she was cyanotic in oxygen and on the seventh day developed signs of pneumonia. On that day, the urine was first noted to have a peculiar aromatic-fetid odor variously described as "caramel," "arginine-like," or (on suggestion) "perhaps maple syrup." A few hours later she died.

At postmortem examination the infant was found to have marked cyanosis and edema, with small amounts of serous fluid in the pleural, peritoneal, and pericardial sacs. The heart weighed 29 grams and showed mild interstitial edema. There was bilateral bronchopneumonia, with patchy areas of atelectasis, moderate esophagitis, and severe fatty degeneration of the liver with brown pigment deposits in some areas. The kidneys were congested and intracellular inclusion bodies were found in some areas; these were also present in the thymus. The brain weighed 420 grams and contained areas of pale vacuolated cells in the white matter.

CHROMATOGRAPHY

A urine specimen, obtained immediately prior to death, was examined by the two-way filter paper method of Dent[8] and by the ion exchange column of Moore, Stein, and Spackman[9, 10]

The filter paper chromatogram (Fig. 1) showed massive amino aciduria for valine and leucine-isoleucine. The other amino acids showing moderate increases were: methionine (as sulfoxone), cystine (as cysteic acid), taurine, threonine, aspartic acid, histidine and phenylalanine. An unidentified ninhydrin-reacting substance was also present. Tyrosine did not appear on the papers.

The significant portions of the tracing obtained by the column method are reproduced in Fig. 2, in comparison with that of a representative normal 13-day-old female infant. It depicts a conspicuous excess of valine, leucine, isoleucine, and methionine. The first three are characteristic of this disease when they occur in such excess over other amino acids and the fourth has been present in most other cases. Fowler[11] reported an unknown substance which may interfere with valine on the column in small infants, but comparison with the filter paper method leaves little doubt that, in this instance, the substance is valine.

Moderate amounts of tyrosine and phenylalanine were found. Though small amounts of these acids often appear at this age, those found here appear to be increased considerably outside the normal range. Elevated levels have not previously

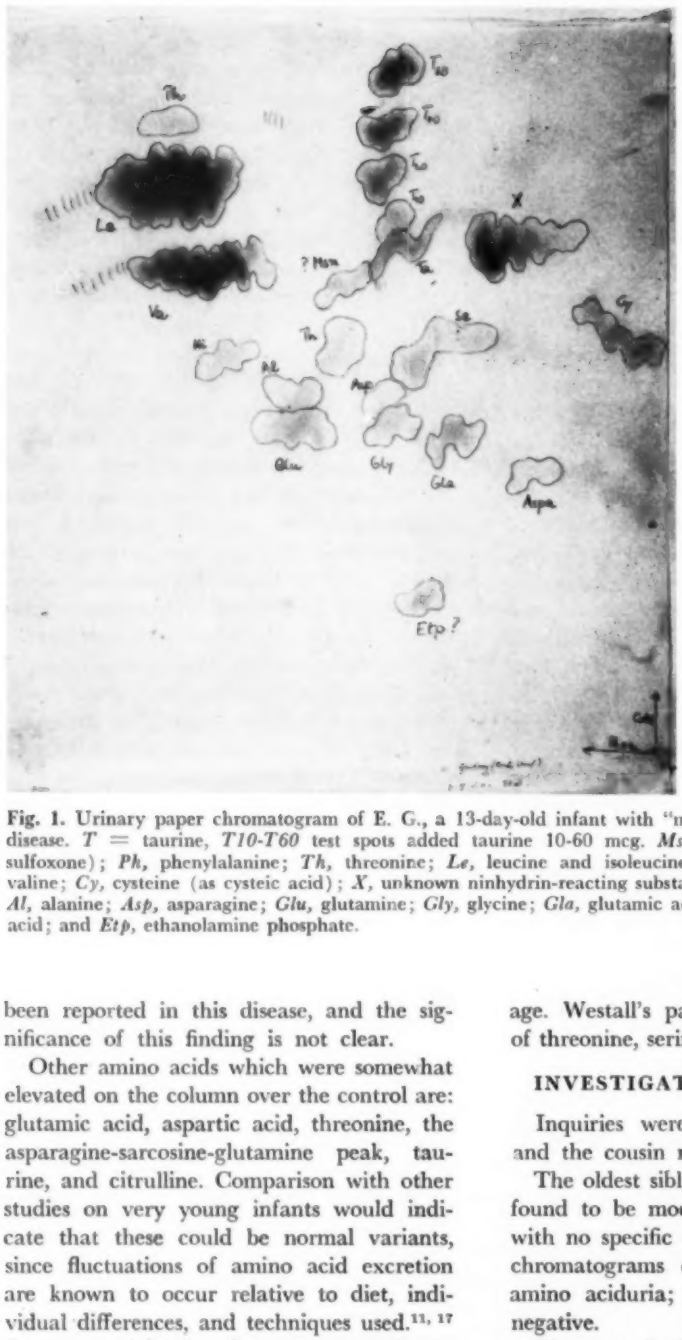

Fig. 1. Urinary paper chromatogram of E. G., a 13-day-old infant with "maple syrup urine" disease. *T* = taurine, *T10-T60* test spots added taurine 10-60 mcg. *Msn*, methionine (as sulfoxone); *Ph*, phenylalanine; *Th*, threonine; *Le*, leucine and isoleucine; *Se*, serine; *Va*, valine; *Cy*, cysteine (as cysteic acid); *X*, unknown ninhydrin-reacting substance; *Hi*, histidine; *Al*, alanine; *Asp*, asparagine; *Glu*, glutamine; *Gly*, glycine; *Gla*, glutamic acid; *Aspa*, aspartic acid; and *Etp*, ethanolamine phosphate.

been reported in this disease, and the significance of this finding is not clear.

Other amino acids which were somewhat elevated on the column over the control are: glutamic acid, aspartic acid, threonine, the asparagine-sarcosine-glutamine peak, taurine, and citrulline. Comparison with other studies on very young infants would indicate that these could be normal variants, since fluctuations of amino acid excretion are known to occur relative to diet, individual differences, and techniques used.[11, 17] It seems certain that they are not a primary feature of the disease and, if not physiologic, may be due to secondary renal damage. Westall's patient[20] had lowered levels of threonine, serine, and alanine.

INVESTIGATION OF THE FAMILY

Inquiries were made regarding siblings and the cousin mentioned in the history.

The oldest sibling was examined. She was found to be moderately retarded mentally, with no specific neurological picture. Paper chromatograms of her urine revealed no amino aciduria; a ferric chloride test was negative.

The second sibling and the cousin had died with histories somewhat similar to that of the patient described here.

The second sibling was admitted to another hospital when 8 days old with the complaints of cyanotic attacks, listlessness, and failure to nurse. She weighed 6 pounds and 9 ounces and was in extremis, with irregular, labored respirations. She was given Synkamin and oxygen. The hemoglobin was 16 Gm. per cent and the white and differential blood cell counts were normal. The urine was acid and contained a trace of albumin but no sugar, diacetic acid, or acetone. There were many epithelial cells and occasional white blood cells, red blood cells, and granular casts in the urinary sediment. Chest x-ray showed mediastinal widening and a "prominent" heart. Spinal fluid contained 2 white blood cells and 2 red blood cells per cubic millimeter; the Pandy reaction was 3 plus.

Episodes of cyanosis and "stiffness" alternating with muscular flaccidity and listlessness characterized her hospital course. Terminally she vomited her feedings, became persistently listless, and developed edema about the eyelids. Her breathing became slow and irregular and the urine was noted to be concentrated, "with a strong odor." Subdural taps, done shortly before death, were negative.

The paternal first cousin was found to have the same name as the maternal family and was known to the parents as "related" to the mother. She was born of a normal pregnancy, labor, and delivery. The neonatal nursery course was uneventful, and she was discharged at 3 days of age. Thirty-six hours later she became lethargic, would not nurse, and had many tremors. She was readmitted 48 hours after discharge.

The infant was irritable, the fontanels were bulging, and the cranial sutures were slightly separated. No Moro reflex was present. Urinalysis was negative. Blood counts were normal. Admission spinal fluid showed only many crenated red blood cells. Skull x-rays were negative and subdural taps yielded no fluid. During her hospital stay she had alternating periods of flaccidity and spacticity, but the Moro remained absent. Pupils reacted sluggishly to light. The pulse was slow and irregular. Blood pressure ranged from 50/20 to 75/40. Respiration, normal on admission, became irregular after 24 hours. Rectal temperature ranged from 100.4° to 101.8° F. Her cry, at first high pitched and shrill, later became whiny. Although vomiting ceased after the initial spinal tap, she required parenteral and tube feedings. From the third hospital day, attacks of apnea and cyanosis, sometimes lasting 5 to 10 minutes, occurred. The urine was noted to have a "strong" odor not suggestive of maple syrup, even in retrospect. Five days after admission her breathing became irregular, she grew very lethargic, and the periods of apnea and cyanosis lengthened. The fontanels became tense; bleeding occurred from the nose. A repeat spinal tap yielded yellow fluid with 18 mononuclear cells per cubic millimeter. The patient died on the seventh hospital day, and no autopsy was performed.

DISCUSSION

A comparison of this case with those previously reported leads to a confirmation and amplification of the clinical picture originally noted.

The intermittent flaccidity, which was so striking a clinical feature in this case, has not been mentioned before. In the 7 well-documented cases, rigidity, either constant

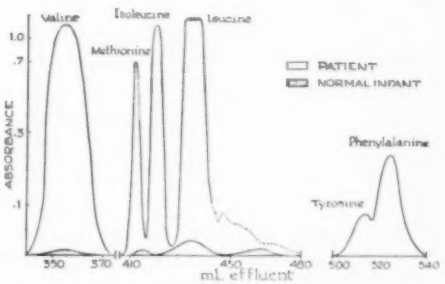

Fig. 2. A composite drawing of significant sections of the urinary amino acid column chromatogram of E. G., in comparison with that of a normal 13-day-old baby girl, showing the conspicuous elevations of valine, leucine, isoleucine, and methionine characteristic of "maple syrup urine" disease, and an unexplained elevation of tyrosine and phenylalanine.

or intermittent, has been a prominent feature. Associated tonic and minor motor seizures have been found in 3, generalized convulsions in 2, and opisthotonus in 3. Other signs of central nervous system depression—lethargy, absent Moro reflex, weak cry, and failure to nurse, have been noted in all cases. The latter was a frequent presenting complaint. Developmental retardation has been present in all infants surviving over 6 weeks. Bronchopneumonia has been a frequent terminal complication.

The respiratory depression and irregularity, with or without cyanosis, is an almost constant feature. In this patient although the irregularity suggested the Cheyne-Stokes pattern, it was different, consisting of periods of apnea interspersed with deep, cogwheel gasps.

In the differentiation from birth trauma, the 3 to 14 days' delay in onset of symptoms is useful. Subdural hematoma and hypocalcemic tetany, which might present thus, can be easily excluded. A family history of similar neonatal deaths, if present, is also helpful.

Perhaps because of the emphasis on the urinary odor for recognition, all reported cases have had this feature at some time in the course of the disease, though it often appears late. In this case it is doubtful if the diagnosis could have been made from this alone, as only one of six observers would agree that the odor was characteristic of maple syrup. MacKenzie[3] has made a similar observation. In our experience, however, and as mentioned by the same author, the odor became much more marked after freezing, and this constitutes a useful clinical maneuver. Further confusion may arise from cases such as Smith and Strang's,[4] in which the urine had a suggestive odor, but chemical findings were different. It would seem desirable to investigate urines of infants with suggestive neurological disturbances by chromatography. For this purpose, two-dimensional paper chromatography is probably the simplest reliable method.

The presence of large amounts of valine, isoleucine, and leucine, and frequently methionine is definitive. However, in one case[1] where the clinical picture and odor were present urine chromatography yielded a normal amino acid pattern. In another patient[2] one sample had only keto acid derivatives of the characteristic amino acids, while another showed the usual pattern.

The autopsies have so far failed to reveal any characteristic changes.

The similarity to phenylketonuria has led recently to a trial of management with a synthetic diet which showed promise in one patient.[18]

Genetic studies on this family are in progress. The association of 2 possible cases in this sibship and another in a double cousin would be consistent with a simple recessive trait. Although the condition of the oldest sibling may be merely coincidental, the question arises as to whether a variant of this metabolic error might not produce mental deficit without significant amino aciduria.

SUMMARY

An example of "maple syrup urine" disease was confirmed by amino acid chromatography; its description is accompanied by a summary of the clinical features found in other reported cases. The characteristic pattern is that of an infant who, after thriving for the first few days of life, begins to nurse poorly, develops progressive depression of respiration, and exhibits rigidity, often intermittent or alternating with periods of remarkable flaccidity and depression. The downward course ends in death at from 2 weeks to 20 months of age. Though a peculiar odor has always been present in the urine, it may occur late and may not be easily identifiable as "maple syrup."

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Methylene blue induced cyanosis and acute hemolytic anemia complicating the treatment of methemoglobinemia

Nathan Goluboff, M.D.,* and Ross Wheaton, M.D.

SASKATOON, SASKATCHEWAN

METHYLENE blue (tetramethylthionine chloride) has been recommended and used frequently for the treatment of methemoglobinemia. In pediatric practice it has been used most often in the treatment of infants suffering from cyanosis caused by the ingestion of well water containing nitrates.[2-4]

Unusual or toxic effects following intravenous methylene blue have rarely been referred to in the numerous publications on methemoglobinemia.[1, 4, 5] The possibility that hemolytic anemia is caused by methylene blue has been discussed occasionally.[5, 6] The presence of a prolonged blue-gray discoloration of the skin has not been reported previously to our knowledge.

The following report will include the case histories of 2 infants who have shown toxic effects following the administration of methylene blue. Certain aspects of this toxicity will be discussed.

CASE REPORTS

Case 1. A white male infant 1 month old and weighing 7 pounds was admitted to the Saskatoon City Hospital at 2:30 P.M., June 25, 1958. Thirty-six hours prior to admission the infant who had previously been breast fed was changed to a partly skimmed, evaporated milk formula of equal parts of milk and well water. Twenty-four hours later a bluish coloration of the skin was noted by the parents. Moderate diarrhea and a general listlessness had been present for several days. Shortly after admission the hemoglobin concentration was 16 Gm. per cent with 50 per cent methemoglobin by spectrophotometric estimation. At 3 P.M. 1 c.c. of 5 per cent methylene blue was administered intravenously instead of the usually recommended 1 per cent solution. The infant remained a very dusky blue. At 4:30 P.M. he voided bright blue urine.

By 10 P.M. there was no improvement in the child's color or condition. The respiratory rate was 70 per minute. The infant was placed in a Croupette with oxygen and given an additional 0.75 c.c. of 5 per cent methylene blue intravenously. On June 26 the infant was still very blue and lethargic. A repeat spectrophotometric determination was carried out and this disclosed no abnormal hemoglobin. Moderate diarrhea continued. On June 29 the blue-gray cyanosis finally disappeared 4 days after the initial injection of methylene blue.

*Address, 105 The Medical Building, 217 3rd Avenue North, Saskatoon, Saskatchewan.

The infant was noted to be mildly jaundiced on June 30; on July 3, he appeared very pale. Examination of the blood at this time disclosed the following: hemoglobin 5.1 Gm. per 100 c.c., red blood cells 1.8 million, color index 0.92, nucleated cells 17,150, polymorphonuclear leukocytes 21.5 per cent, bands 7 per cent, lymphocytes 34 per cent, monocytes 9 per cent, eosinophils 6.5 per cent, and normoblasts 22 per cent.

The serum bilirubin level on July 4 was 2.3 mg. per 100 c.c. serum; the Coombs test was negative. A blood transfusion was given on this date. Diarrhea continued until July 10. The infant was discharged from the hospital July 18, with a hemoglobin level of 11.9 Gm. per 100 c.c.

The well water used by the parents in preparation of the formula was found to contain 900 p.p.m. of nitrates.

Blood estimation for genetic defects of glucose $6PO_4$ dehydrogenase and 6-phospho glucodehydrogenase were reported as normal.*

In view of the paucity of reports on methylene blue overdosage and the prolonged cyanosis and hemolytic anemia resulting from such overdosage in Case 1, it was felt that the purposeful duplication of this picture, if possible, would be of great value.

Case 2. This white male infant was born Feb. 4, 1960, weighing 5 pounds, 2 ounces, and was severely microcephalic. The child was otherwise normal. Permission from the parents permitted the following procedure to be carried out.

At 10:30 A.M. on Feb. 17, at 2 weeks of age and weighing 4 pounds, 10 ounces, 0.75 c.c. of 5 per cent methylene blue was injected intravenously over a period of several minutes. Following this the child became markedly bluish, which is similar to what is seen in methemoglobinemia. Twenty minutes after the injection a sample of blood was taken but no abnormal hemoglobin was present. Methylene blue, however, was demonstrated spectrophotometrically to be present in the blood. One hour after the initial injection the color had gradually improved and by 1 P.M. there was only a mild grayish blue appearance. At this time another 0.75 c.c. of 5 per cent methylene blue was injected intravenously. Soon afterward the infant became markedly grayish blue in color. There was some slight improvement about 1:30 P.M.; however, by 2 P.M. the whole body except the ears (which remained pinkish) again became more severely grayish blue. The bridge of the nose and skin above the nostrils became increasingly bluish, as though stained with methylene blue.

The voided urine 15 minutes after the initial injection was clear. Subsequent urine over the next 4 days was blue in color. Occasional twitching was noted during the night, and the infant fed poorly for several days. Otherwise the condition remained unchanged except for the ghastly color.

On February 18 the infant was still very blue. Pressure on the skin of the feet and other areas revealed a bluish appearance of the blanched skin. Spectrophotometric studies of the blood on this date (24 hours following methylene blue injection) disclosed no abnormal hemoglobin and no methylene blue.

On February 21 (4 days after the injection) the infant's color approximated normal after he had appeared cyanotic for almost 4 days. February 19, the hemoglobin was 17.6 Gm. per 100 c.c.; on February 20, it was 16.3 Gm. per 100 c.c., and on February 21, the infant appeared somewhat jaundiced. On February 22 serum bilirubin was 11.3 mg. per 100 c.c. serum (direct 0.9, indirect 10.4); hemoglobin 14 Gm., red blood cells 4.34 million, white blood cells 20,300. The differential count was polymorphonuclear leukocytes 21 per cent, bands 3 per cent, lymphocytes 46 per cent, monocytes 24 per cent, eosinophils 5 per cent, metarubricytes 1 per cent, and reticulocytes 5 per cent. All the red blood cells when stained supravitally with methylene blue for reticulocytes contained a mass of blue-staining material.

February 24, the hemoglobin estimation

*Performed by Dr. D. W. Zinkham at The Johns Hopkins Hospital.

was unsatisfactory because of resistance of erythrocytes to osmotic hemolysis. The infant appeared pale. February 26 the hemoglobin was 8.6 Gm. per 100 c.c., red blood cells 2.59 million, white blood cells 12,400. The differential count was polymorphonuclear leukocytes 25 per cent, bands 4 per cent, normoblasts 1 per cent, lymphocytes 49 per cent, monocytes 14 per cent, eosinophils 6 per cent, and reticulocyte count 7.8 per cent. Further blood estimations were not made until March 9 when the hemoglobin was 7.3 Gm. per 100 c.c. and the reticulocyte count was 11 per cent. No treatment was given but gradually the hemoglobin rose to 10.4 Gm. per 100 c.c. on March 21. The reticulocyte count was 3.2 per cent.

DISCUSSION

The recommended dosage of methylene blue in the treatment of methemoglobinemia is 1 to 2 mg. per kilogram of body weight.[1, 4]

Nadler and co-workers,[7] in discussing toxic effects of methylene blue intravenously, noted that the prevailing impression was that no more care was needed than in intravenous injection of saline. They injected 18 normal adults with 50 c.c. of 1 per cent solution of methylene blue intravenously. It took 3 to 5 days for the drug to be eliminated. Electrocardiograms demonstrated in every case a great reduction in height of the T wave, and also a decrease in the R wave. There was a slight increase in the respiratory rate, a sense of oppression in the chest, and some difficulty in breathing. There was moderate acceleration in the heart rate but no change in the blood pressure. Soon after the injection was started, the skin and mucous membranes became bluish. This was apparently very transitory. Restlessness, apprehension, and fine fibrillary tremors of the face and extremities developed. There was occasional nausea and vomiting of blue-stained fluid. The saliva was also tinted blue. Hemolytic anemia did not develop.

Bodansky[4] in his comprehensive article on methemoglobinemia discusses a case reported by William and Challis, in which an adult patient, intensely cyanosed and semi-comatose, responded dramatically within an hour after intravenous administration of 100 c.c. of a 1 per cent solution which is equivalent to 15 mg. of methylene blue per kilogram. He points out that the dose was unnecessarily high, but that this case incidentally illustrates the relatively nontoxic nature of methylene blue.

The 2 infants presented in this report were given an overdose of methylene blue, Case 1 unknowingly and Case 2 purposefully. In Case 1 the infant should have received 6 mg. or less (0.6 c.c. of 1 per cent solution). Instead he initially received 50 mg. (1 c.c. of 5 per cent solution) or a dose of over 15 mg. per kilogram of body weight, followed 7½ hours later by a further dose of 33 mg. In Case 2 the dosage was slightly in excess of that in Case 1.

Both infants developed a bluish-gray coloration which persisted for about 4 days, and in addition both developed an acute hemolytic anemia. The former simulates the appearance of methemoglobinemia and can quite easily lead to further administration of methylene blue from the mistaken conclusion that methemoglobinemia was persisting.

Methylene blue hemolyzes mammalian red blood cells on oral or parenteral administration[5, 11] as well as in vitro, probably by changing the glucose metabolism with decreased oxygen consumption[5, 9, 10] and often with Heinz body formation.[5] Actual cases of severe hemolytic anemia in humans caused by methylene blue have not been previously reported to our knowledge.

Mangelsdorff[3] is one of the few authors who has stressed the complication of hemolytic anemia, although it did not occur in his own reported cases. He stated, however, that he felt the only justifiable use for a drug or a dye as dangerous as methylene blue would be in cases of methemoglobinemia with an extremely high methemoglobin (over 60 per cent), where rapid reduction of the methemoglobinemia would be an advantage, and then only the use of small amounts to hasten the reduction.

Methylene blue after injection is distributed through all the body tissues, but it is rapidly reduced to colorless leuko compounds. These are oxidized when tissues are exposed to air, or are in contact with hydrogen peroxide, thus restoring the blue color. According to Sollman,[8] prolonged ingestion gives a blue tint to the vitreous humor, this being the only tissue in the body which is blue before exposure to air.

It appears probable to us that in small infants the enzymatic process converting methylene blue to the leuko form does not proceed rapidly enough, and that it takes at least a few days until methylene blue is either converted to the colorless form or excreted from the body.

Methemoglobinemia in infants resulting from ingestion of well water containing excess nitrate is relatively frequently encountered in some areas. Methylene blue intravenously is of great value in severe cases, but should be administered in proper dosage and with caution.

In pediatric practice it appears, from the paucity of reports of toxicity, that in recommended dosage the danger of toxic effects or of abnormally induced cyanosis is very minimal. Since methylene blue does come in 5 per cent ampules, one must be very careful to estimate the proper dosage in milligrams per kilogram or pounds and preferably use a 1 per cent solution, in which case 0.5 to 1 c.c. will generally be quite safe.

CONCLUSION

Intravenous administration of methylene blue in infants in large dosage can cause: (1) a generalized bluish-gray discoloration (cyanosis) which may persist for 3 to 4 days and (2) an acute hemolytic anemia which is manifest about a week later.

Methylene blue should be administered only intravenously with great care in regard to dosage and with realization of its potential toxicity.

SUMMARY

Case histories of 2 infants who received large doses of intravenous methylene blue have been reported. One infant received the large amount during treatment for well water methemoglobinemia. The other infant was given a similar dose experimentally.

The skin of both infants turned a grayish blue and remained so for about 4 days following administration of methylene blue. This phenomenon has not been previously described. Both children developed an acute hemolytic anemia about a week later.

These toxic effects of methylene blue overdosage have been discussed. It has been stressed that methylene blue is not an innocuous drug and, though of great value in the treatment of methemoglobinemia, recommended dosage should not be exceeded.

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Anaphylaxis following ingestion of soybean

Edna Z. Mortimer, M.D.*

CHICAGO, ILL.

THERE are few reported cases of severe reaction[1] following ingestion of soybean, and even fewer reports of shock or of anaphylaxis. Recent awareness of an increasing number of infants and children in our clinic with positive skin tests to soybean and of some with clinical manifestations of allergy after ingestion of soybean has occasioned special interest.

CASE REPORT

M. M., a Negro male, 6 pounds, 8 ounces at birth, was brought to the clinic in January, 1956, when he was 3 months old. Eczema had been present for 2 months and was now becoming generalized and severe. His weight at this time was 12 pounds, 5 ounces. The family history was positive for allergy: asthma, father and paternal grandmother; allergic bronchitis, 1 sibling; hay fever, 2 paternal aunts; and eczema, 1 paternal aunt. The baby had been breast fed for his first month but during this time had also been given evaporated milk and homogenized whole cow's milk. At the initial visit hypoallergenic and prophylactic measures were instituted and he was given a soybean formula (Sobee). Two months later he developed asthma. From the very beginning, the mother reported a great deal of vomiting in relation to the soybean formula: 3 soybean brands were tried and with each one the rash was made worse and there was more mucus. When the soybean formula was omitted the baby improved. The scratch test for soybean was mildly positive and the intradermal test was 4 plus. The baby was put on Nutramigen which he tolerated well. He showed dramatic improvement of the eczema and some improvement of the asthma; when he was 18 months of age the eczema had completely cleared.

Two months after this the patient was hospitalized for acute febrile pharyngitis with otitis media. He was admitted at noon, having received no feeding or medication except for weak tea in the preceding 12 hours. Achromycin was started for the infection. The first food he received, inadvertently, was a soybean formula and he promptly went into shock. There were respiratory collapse and feeble heart tones. He was placed in oxygen, given Adrenalin and caffeine-sodiobenzoate, and intravenous fluids containing ACTH. His respirations improved but he remained unresponsive with reflexes absent for about an hour, after which he began to respond to stimulus; within 3 hours he was awake. Improvement continued and by the following noon he took feedings of Nutramigen eagerly. The parenteral medications were stopped after 48 hours and were continued orally. At the end of one week he was considered recovered from the initial infection and the inadvertent shock.

This paper was presented before the Ninth International Congress of Pediatrics, Montreal, Quebec, July, 1959.

**Address, The Children's Memorial Hospital, 707 W. Fullerton Avenue, Chicago 14, Ill.*

Laboratory and clinical data. This child subsequently was followed in the Allergy Clinic where additional data were obtained pertinent to confirming the original clinical diagnosis. First, it was learned that prior to and for 2 years after his birth the family lived in the immediate vicinity of one of the largest soybean processing plants in the country, thus providing ample opportunity for exposure to soybean dust. The family was advised to move from this environment, and did so.

Prausnitz-Küstner passive transfer tests were done in April and May, 1959, almost 2 years after the anaphylactic reaction. Seven nonallergic subjects were skin tested to rule out hypersensitivity to soybean, and served as recipients for the test. The patient's serum was injected to determine the presence of circulating antibodies specific to soybean. The passively sensitized areas were tested directly 48 to 72 hours later (1 subject at 96 hours). Positive skin reactions appeared at the prepared site in 5 of the 7, indicating that the serum of this patient did contain circulating antibodies for soybean.

The bronchoscopic report described the typical mucosal appearance of allergic bronchitis—the smears from the secretions showed 4 per cent eosinophils. Periodic blood counts were normal except for eosinophilia, which ranged from 6 to 34 per cent. Blood chemistry determinations revealed that nonprotein nitrogen, globulin, albumin, phosphatase, cholesterol, and cholesterol esters were all normal. The serum electrophoresis pattern was normal; the examination of the stool for trypsin was normal; sweat electrolytes were negative; chest x-ray, and electrocardiogram were normal.

The soybean skin test (intradermal) which was done when the patient was 8 months old was 4 plus. The test was strongly positive when the child was 3 years old. The possibility that the test might have caused a repetition of the anaphylactic shock was fully understood. However, there was no untoward clinical reaction. To test further the belief that allergenicity diminishes with avoidance of the antigen, a soybean milk (1:2) was given to the patient starting with 1 ounce once or twice weekly, and gradually increased to 6 ounces. There was no reaction.

DISCUSSION

Skin tests have been done on 220 allergic infants and children: 93 from the Children's Memorial Hospital Allergy Clinic and 127 from private pediatric allergy practice. Only those with definite and marked whealing were accepted as positive reactions. Intradermal tests were done if the scratch tests were negative or weakly positive. Twenty-three (25.8 per cent) of the clinic patients had positive reactions; 34 (26.7 per cent) of the private pediatric patients had positive reactions. Using the same antigen, Dr. Sam Untracht tested allergic children at the Pediatric Allergy Clinic of Metropolitan Hospital, New York, and reported that 15 per cent of these patients showed definite wheal reactions.

It would appear from these observations that in an allergic pediatric population, positive skin tests to soybean are significantly high. At the present time in this study the correlation of positive skin tests with the clinical manifestations of allergy are approximately 7 per cent.

It is interesting in this connection to refer to the figures on cow's milk allergy. As given by Clein[1] and Glaser[2] it is about 7 per cent in practices composed of allergic and nonallergic infants. However, Susan Dees[3] has made 2 separate studies on allergic and nonallergic infants of similar age groups and reports a much higher percentage; it was 30 per cent among allergic infants with a 37 per cent positive skin test correlation, as compared to 1 per cent among nonallergic infants.

In the 30 years since soybean products have been introduced for infant feedings, soybean allergenicity appears to be increasing in the allergic child. Hill[4] deduced from his studies 17 years ago that soybean was a poor antigen. Ratner[5, 6] undertook to investigate soybean from the standpoint of its allergenicity in the human subject and its anaphylactogenicity in the guinea pig, and came

to similar conclusions, noting that the chief hazard from the standpoint of allergy would seem to be that of inhalation of soybean dust. Also, Glaser[7] in 1944, while stating that the various soybean milks have been of tremendous value in the feeding of infants sensitive to cow's milk, found nevertheless, an occasional infant allergic to Mull-Soy. Thus, 15 years ago, sensitivity to soybean milk was considered rare but Glaser made the comment that with the tremendous increase in the use of soybean as an article of diet and as a basis for plastics and countless other products, sensitivity to soybean will surely become more and more common.

In connection with the present widespread use of soybean it is interesting to note the geographic variations in the incidence of reported clinical sensitivity. The Midwest, especially the Greater Chicago area, has the greatest concentration of soybean processors in America. This difference in the geographic distribution of soybean may account for the wide divergence of reports of soybean allergenicity in the pediatric age groups. This was clearly shown by personal communications for all sections of the country in response to a request for this information. However, these reports of geographic variations should be further investigated to determine to what extent soybean is used as a substitute formula by pediatric allergists. For example, the incidence of soybean allergy may depend upon the frequency with which soybean milk is used as a substitute food in pediatric practice and clinics.

While the incidence of soybean allergy in children may be increasing, few severe reactions have been reported and true anaphylaxis has been exceedingly rare. In an adult, the case of Duke[8] in 1934 was probably the first such case to be reported. In 1948, Wergeland[9] of Copenhagen cited the case of an infant which he described as anaphylactic shock following the introduction of soybean formula. In 1953, von Vest[10] of Germany reported a very complicated case of an infant who went into shock after ingestion of cow's milk and again after soybean milk.

SUMMARY AND CONCLUSIONS

A case is presented of true soybean anaphylaxis in an allergic infant with asthma and eczema. The skin test for soybean was markedly positive, correlating with the clinical findings and with the subsequent prompt improvement, especially of the eczema, when soybean feedings were discontinued. Passive transfer tests were positive after 2 years, indicating a sufficiently high soybean antibody titer.

In view of recent evidence and the report of the present case, it appears there should be a re-examination of the allergenicity of soybean which until now has been considered a weak antigen. Will the continued increased exposure of the general population to soybean and its many preparations change its status so that soybean may eventually approach cow's milk as a potent antigen?

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TROPICAL PEDIATRICS

Hospital admissions for pediatric accidents in Upper Assam

C. V. Foll, M.R.C.S., L.R.C.P., D.T.M.&H., D.(Obst.)R.C.O.G.*

ASSAM, INDIA

IT HAS recently been stated that the problem of accidents in tropical children warrants more attention than has been given it.[1] All "accident" admissions to the pediatric wards of the Assam Oil Company Hospital in Digboi, Upper Assam, during 1959 have been analyzed, and, in addition, all children admitted suffering from burns or scalds or from poisoning during the 6 year period of 1954 to 1959 have also been studied. It is realized that such an analysis of hospital admissions for accidents will produce some bias since only the more serious cases will be admitted and since factors such as the number of available beds, willingness of parents to leave their children in the hospital, facilities available at the particular hospital, and the method of treatment (i.e., applying plaster of Paris to fractures in the outpatient department or with the child as an inpatient) will all influence the cases discussed in this series. From these analyses, however, although the number of cases involved is not very large, it is hoped to give some indication of the present pediatric accident pattern in this part of Assam, and hence provide a background against which an accident prevention program may ultimately be planned.

From the Assam Oil Company, Ltd., Digboi, Assam, India.

**Address, c/o Burmah Oil Company (B.T.) Ltd., 604 Merchant Street, Rangoon, Burma.*

THE PATIENTS AND THEIR ENVIRONMENT

The 132 children in the first part of this study are predominantly the children of the 7,500 Assam Oil Company employees and include Assamese, Bengalis, Nepalis, Madrasis, Punjabis, Gorokhpuris, and so on. The 132 admissions for accidents may be compared with 34 admissions for acute nephritis, 38 for whooping cough, 26 for diphtheria, 9 for malaria, 20 for tuberculosis, and 67 for measles during the same period of time. Accident cases represented 10.1 per cent of the total admissions to the pediatric wards.

Digboi is a town with a population of approximately 50,000 persons, and lies in the northeast corner of Assam. The fathers of the children are employed in the oil fields, refinery, or auxiliary services, and their socioeconomic status ranges from unskilled to skilled. Children of more senior employees are excluded from the series because the

Table I. Accidents in Digboi during 1959

Type of accident	*Boys*	*Girls*
Burns	16	10
Poisoning	11	4
Trauma		
Traffic	18	4
Other	42	17
Miscellaneous	8	2
Total	95	37
Ratio of males to females	2.6	1

Table II. Type of accident and age group involved

Type of accident	*Age (years)*			
	Under 1	*1-5*	*5-10*	*10+*
Burns	0	18	6	2
Poisoning	1	14	0	0
Trauma				
Traffic	1	3	10	8
Other	2	14	24	19
Miscellaneous	0	4	3	3
Total	4	53	43	32

Table III. Racial incidence of accidents

Race	*Assamese (%)*	*Bengalis (%)*	*Nepalis (%)*	*Others (%)*
Labor force	27.8	21.2	22.0	29.0
Admissions	39.5	11.9	26.7	21.9
Burns	34.6	26.9	30.8	7.7
Poisoning	26.7	13.3	40.0	20.0
Traumatic accidents				
Traffic	54.5	9.1	27.3	9.1
Other	47.5	8.5	23.7	20.3
Miscellaneous	80.0	20.0	0	0
All causes	46.2	13.7	25.7	14.4

Table IV. Poisonings in Digboi (1954 to 1959) and Nagpur (1954 to 1958)[3]

Group	*Digboi*		*Nagpur*	
	No. of cases	*%*	*No. of cases*	*%*
Medicaments	10	11.4	13	16.2
Household poison	75	85.2	37	46.3
Poisonous plants	3	3.4	26	32.5
Miscellaneous poisons	0	0	4	5.0

number involved is too small to be of significance. The population under study may be considered an urban one.

A temperature range of about 102° to 46° F. is experienced during the year (the average maximum temperature in July was 93.61° and the average minimum temperature in December was 53.55° F.). During the year there were 117 inches of rain.

TYPE OF ACCIDENT AND SEX OF CHILD INVOLVED

The accidents may conveniently be divided into 4 main groups: burns, poisonings, trauma, and miscellaneous. The trauma group may again be subdivided into trauma associated with traffic, and trauma not so associated. Table I gives these details.

The predominance of boys (72.1 per cent) is in accordance with the ratio in other accident series and will be discussed later.

Age. If an arbitrary division is made into 4 age groups (under 1 year, 1 to 5, 5 to 10, 10+) the age incidence in the various groups may be demonstrated.

From Table II, it may be seen that the majority of burns and poisoning cases occur between the ages of 1 and 5 years, while the majority of other accidents occur after the age of 5 when the child is more mobile and more likely to be injured at play (i.e., falling from trees, football, cycle accidents, and the like). This pattern is very similar to that seen in nontropical countries.

The over-all sex ratio of males to females was 2.6:1. The sex pattern is of interest because it is found that up to the age of 5, 35 accidents occurred in boys and 22 in girls; after 5, the predominant incidence in boys was very marked: 61 as compared to 14 in girls. This pattern has been shown in other series: for example, in Toronto, Fowler[2] in a summary of 150 accident cases in private pediatric practice found that there were 30 males and 34 females under 3 years of age, and there were 61 males and 25 females above 3 years of age. There are several reasons for this: First, up to the age of 5 years, boys and girls are equally active and equally liable to have traumatic acci-

dents; second, after this age boys may be more adventuresome and girls more cautious; third, Indian tradition restricts girls to household duties where they have to assist their mothers.

Ethnic group. As already mentioned, peoples of various ethnic groups live in Digboi, and in order to see if any particular one is more prone to a particular accident, it is necessary to compare the percentage of that total accident per group with the percentage of total admissions per group. Table III gives these details. "Others" include children from Southern and Central India.

It appears probable that Bengali parents are even more "hospital shy" than the average Indian parents. Many reasons have been suggested by way of explanation for this: There is a traditional handing down of family care procedure from one generation to another; there is a definite suspicion of nurses and doubt as to their ability to care for children; there is also an exaggerated idea of the dependence of these children on their parents; there is a lack of faith in hospitals which is not helped by the frequent newspaper reports of mismanagement; and finally there is a very firm belief in the efficacy of homeopathy, especially for children.

The percentages of the various ethnic groups among the employees is as follows: Assamese 27.8 per cent, Bengalis 21.2 per cent, Nepalis 22.0 per cent, others 29.0 per cent.

Table III shows that Bengalis had more burns, Nepalis more poisonings, and Assamese more traffic accidents than one would have expected. The series is rather small to attach much significance to this, however, and further work may throw more light on these differences.

Traumatic accidents. The traffic accidents involved cars, bicycles, and rickshaws, and the other traumatic episodes included falls from trees, swings, and gates, football injuries, and falls into *nullahs* (ditches). The sex incidence of traffic accidents is of interest since 4½ times as many accidents occurred in boys than in girls. Of the 22 accidents that resulted in the child's being admitted to the hospital, 12 were caused by bicycle accidents. Eleven of these children were boys, one a girl. One very seldom sees a girl on a bicycle; one reason for this is that *saris*, universally worn above the age of 12 with their flowing lengths of cloth, are not the ideal garments for bicycling. There were 3 limb fractures (2 of the ulna and one of the tibia) in this group, the other injuries being multiple abrasions. Cars knocked down 6 of the 22 children and one fell out of a car; a car hitting a rickshaw injured a further 2, while an infant 3 months old fell out of a rickshaw, although her main injuries were caused by her mother's falling on top of her.

Miscellaneous. This group included 2 cases of near drowning and 2 of swallowing coins. Dog, monkey, and goat bite cases were seen fairly frequently, but these patients were not admitted to the hospital.

Mortality. There was one death due to a subarachnoid hemorrhage associated with a fractured skull in a Nepali child of 9 following a car accident.

Table V. Sex incidence in Digboi and Nagpur[3]

Poison	Digboi		Nagpur	
	Boys	Girls	Boys	Girls
Medicaments	6	4	9	4
Household	45	30	29	8
Poison plants	1	2	16	10
Miscellaneous	–	–	3	1
Total	52 (59.1%)	36 (40.9%)	57 (71.2%)	23 (28.8%)

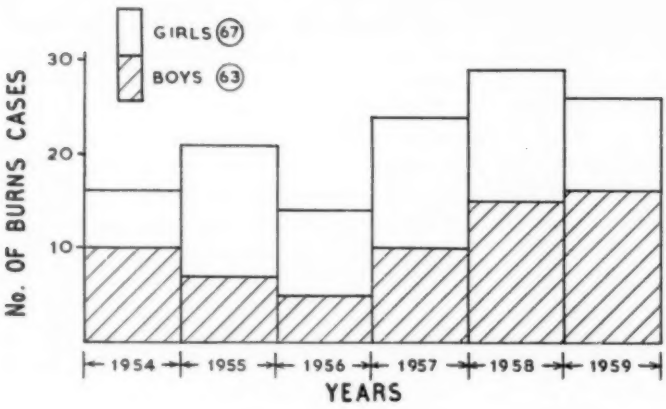

Fig. 1.

BURNS AND POISONING (1954 TO 1959)

In order to study a larger series of cases of severe burns and poisoning, it was decided to analyze all pediatric admissions for these conditions in the years 1954 to 1959, inclusive.

Burns. The yearly incidence of burns and the sex incidence may be seen in Fig. 1 which gives details of the 130 cases in this series.

There is little difference in the sex incidence. A seasonal variation was seen with more cases occurring in the cold weather; this is what one would expect.

Fig. 2 shows the age distribution, and it is noticeable that 86 cases (66.2 per cent) of the total occurred in children under the age of 5 years. This means that the "toddler" is the main sufferer, and, in addition to physical discomfort, has to spend long periods in the hospital at an age when removal from his mother causes the maximum mental trauma. This can be obviated to some degree by encouraging and assisting the mother to visit her child daily.

The distribution of the cases among various ethnic groups was as follows: 45 Bengalis, 38 Assamese, 26 Nepalis, and 21 "others." This confirms the impression from the 1959 series that Bengalis have more cases of burns than one would expect from the total number of Bengali admissions. The significance may be not in more burns but in fewer admissions for other conditions.

In 1959 cases of burns represented 1.9 per cent of all pediatric admissions. Of these 130 patients, 6 died from burns.

Poisonings. In the 6 years (1954 to 1959)

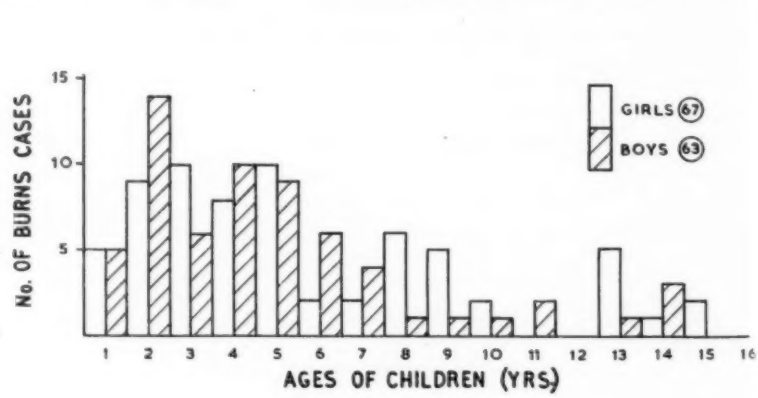

Fig. 2.

under discussion, 88 pediatric patients suffering from accidental poisoning were admitted to the hospital. Of these 88 children, 83 were under the age of 4 (i.e., "crawlers" or "early toddlers"). Mukherji, in an account of 80 poisoning cases seen in the children's unit of the Medical College Hospital, Nagpur (during 4½ years from January, 1954, to June, 1958) found that accidental poisoning accounted for 0.86 per cent of the total admissions[3]; in 1959 in Digboi they accounted for 1.2 per cent of pediatric admissions.

The poisons may be conveniently divided into four main groups: medicaments, household poisons, poisonous plants, and miscellaneous. Table IV shows the incidence of cases in the various groups in Digboi and in Mukherji's[3] series.

Medicaments. This group includes children who took or were given medicine intended for an adult member of the family. The following medicines were taken: Tincture of terebinth by 2 children, Daraprim (pyrimethamine) tablets by 3, calamine lotion by 2, and iodine, zinc oxide, and Dettol each by one.

Household poisons. In our series, kerosene poisoning accounted for 68 cases (77.3 per cent) of the total accidents, as compared with 41.4 per cent in the Nagpur series.[3] Of these 68 children, 48 (70.6 per cent) were under the age of 2 (i.e., crawlers), as compared with 72.7 per cent in the Nagpur cases.[3] Kerosene is the most common and serious cause of poisoning in children in this part of the world (Fig. 3); the high-grade variety is quite colorless and looks like water.

Other poisons in this group included silver paint, turpentine, petrol, phenol, soap, lime, and Dopit (an insecticide).

Poisonous plants. Unlike Mukherji's series, only 3 of our cases are included in this group: 2 due to mushrooms and one to Datura. This group does not appear to be a particular hazard in Upper Assam.

Treatment of kerosene oil poisoning. It has been for many years the accepted practice to wash out the stomachs of children who have swallowed kerosene oil because it was believed that poisoning resulted from kerosene being absorbed through the gastric mucosa. Capel and Gardner[4] refer to recent animal studies by the medical research division of Esso Research and Engineering Company, Linden, New Jersey, where it has been shown that kerosene poisoning is principally due to aspiration of the material into the lungs and that large quantities of kerosene can be ingested without pulmonary injury or ill effect.

Many cases of pneumonic involvement have been seen in Digboi but whether those were caused by aspiration during the vomiting that usually follows ingestion of kerosene oil or during the process of washing out the child's stomach, which is standard treatment in our hospital, is unknown. Antibiotics are given prophylactically.

Sex distribution. Table V shows the sex distribution of the children in the various groups for both Digboi and the Nagpur series. Unlike burn cases, the predominance of boys is marked.

DISCUSSION

The tropical infant and child, already assailed by malnutrition, worms, tuberculosis and anemia, have also to withstand the onslaughts of accidents. Their path to adult life in this respect may be represented diagrammatically as below:

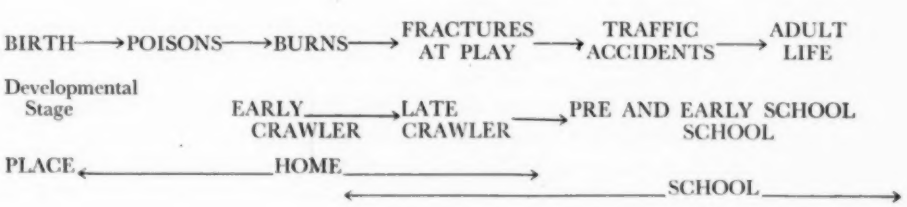

Fig. 3. A typical Assamese kitchen scene (note the kerosene oil tin beside the fire).

The high incidence of poisonings and burns in the younger age groups may be attributed to the fact that Indian women do all their cooking on the floor and it is all too easy for an infant to crawl into danger (Fig. 3). There is also a lack of cupboards, shelves, and storage space in many Indian kitchens and hence everything is stored on the floor, again a temptation to any inquisitive infant. There is little doubt but that some redesigning of Indian kitchens and encouragement to the housewives to cook standing up would have an immediate effect in reducing cases of poisoning and burns.

Traffic accidents, although not the scourge of child life they are in many countries in the West, still cause a number of injuries. As traffic increases there will be a proportionately greater number of child casualties because the roads are at present unsuitable for heavy traffic, there is a complete lack of any traffic sense and discipline, cattle wander indiscriminately on all highways, and there are far too many defective vehicles. Many of the accidents involved bicycles and it is considered that one of the predisposing causes is that children's bicycles are seldom seen. Many children ride adult machines on which they are unable to reach the pedals when seated, and so they ride them leaning sideways with their bodies under the crossbar.

Accident prevention. A World Health Organization Technical Report on Accidents in Childhood published in 1957 states, "The cardinal bases of accident prevention fall into three categories: Education; Engineering; Regulation and Law enforcement."[5]

Education. This must obviously start in the home, and both parents must play their part. Adult education should include lectures on safety in the home. Clements[6] stresses that accident prevention should be taught as a part of mothercraft, while Dietrich[7] has suggested that accident control is a two-phase process comprising protection and education. School teachers should continue and augment the parents' initial efforts. Younger age groups especially will need protection by the placing of a barrier between the child and the danger, and doctors should warn the parents of young children of the particular dangers with which they may meet in individual localities and circumstances.

Engineering. There is a definite need for more kitchen shelves, for raised fireplaces

and for fire screens in this part of the world.

Regulations and law enforcement. This applies particularly in the field of road safety. Traffic education, however, is of little use if no steps are taken to prevent gross breaches of regulations. The cooperation of the police should be sought and an attempt should be made to make children look to the police for help and guidance when traveling to and from school.

Such a preventive program requires little financial outlay but relies mainly on the good sense, enthusiasm, and feeling of responsibility among parents, schoolteachers, police, and not least the children.

SUMMARY

An account is given of the 132 pediatric "accident" cases admitted to an oil company hospital in Upper Assam during 1959. The effect of age and ethnic group is discussed. All pediatric cases of burns and poisoning admitted during the years 1954 to 1959 are analyzed with regard to age and ethnic group. The importance of kerosene oil poisoning is stressed. The predominance of boys in traffic accidents is noted (4½:1). Some aspects of prevention are discussed under the headings of education, engineering, regulation and law enforcement.

I am grateful to Professor R. W. B. Ellis for reading the manuscript and for much helpful criticism and advice.

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The problem of sending fecal specimens to a laboratory for the isolation of pathogenic Escherichia coli in tropical countries

S. D. Suprihatin* and Lie Kian Joe

DJAKARTA, INDONESIA

DIARRHEA among infants is frequent in almost all tropical countries. In Djakarta, Indonesia, infantile gastroenteritis is often associated with the presence of pathogenic *Escherichia coli* in the feces. These bacteria are the most frequent cause of diarrhea among our newborn and young infants. Infections have been found to occur not only nosocomially, but also frequently at home.[1-4] It is possible that pathogenic *E. coli* is also a frequent cause of diarrhea in infants in other tropical countries.

Complete serologic typing of pathogenic *E. coli* is an elaborate procedure which can be done in only a few centers in the world. Preliminary identification of the types, in which only the O antigen group is determined, is easier and less time consuming, but even this procedure cannot be carried out in many tropical areas. A simple and cheap method by which fecal samples could be sent to distant laboratories where preliminary or complete serologic typing of pathogenic *E. coli* can be carried out would promote the study of these infections in many tropical countries.

The dried filter paper technique has proved to be a simple and cheap method for sending certain kinds of fecal specimens to a laboratory. Drying of feces on filter paper has proved to be effective for preserving Salmonella and Shigella.[5-14] With this method it has been possible to send fecal samples wrapped in cellophane or plastic paper in an airmail letter over great distances such as from Indonesia to Holland.

Since we have found pathogenic *E. coli* to play an important role in infantile diarrhea we have also investigated whether the dried filter paper technique could be used for preserving pathogenic *E. coli* and have compared this method with the use of buffered glycerol saline.

MATERIAL AND METHOD

Feces were obtained from diarrheic infants in the Pediatric Department and in the Infant Newborn Nursery of the Central General Hospital in Djakarta. The feces were usually obtained several hours after being passed. They were cultured on Endo agar and on modified Drigalsky agar. Part of the stool sample was dried on filter paper ac-

From the Department of Parasitology and General Pathology, School of Medicine, University of Indonesia, Djakarta, Indonesia.

**Address, Department of Parasitology and General Pathology, University of Indonesia, Salemba 6, Djakarta, Indonesia.*

cording to the technique described previously.[5, 6, 7] The dried feces were kept at room temperature, varying from 24° to 32° C. Most were cultured 1, 3, 5, and 7 days after drying. There was not enough fecal material to perform all these isolations in a number of instances, however. In 96 cases, part of the feces was also kept in buffered glycerol saline.

RESULTS

For this study there were 187 specimens positive for pathogenic *E. coli*. The dried feces kept for one day at room temperature gave 135 isolations. This was about 28 per cent less than the results obtained from the fresh specimens on the previous day. The 52 negative dried fecal samples were discarded. There were 129 specimens of 3 days old dried feces available, which gave 105 isolations. The negative samples were again discarded. From 97 specimens kept for 5 days in a dry condition, 72 were positive and from 70 specimens kept for 7 days, 62 were positive. The serotypes isolated in these studies are shown in Table I.

In Table II are given the results of the dried filter paper technique compared with the use of buffered glycerol saline. The results obtained from buffered glycerol saline are somewhat better than those obtained from the dried feces.

DISCUSSION

The dried filter paper technique employed for preserving pathogenic *E. coli* is not as good as for the preservation of Salmonella and Shigella. Salmonella could be detected in 86 per cent of the cases from 3 days old dried feces and in 83 per cent of the cases with 5 days old feces.[8] Shigella could be isolated from 3 days old dried feces in 78 per cent of the cases, from 5 days old feces in 60 per cent of the cases and in 7 days old feces in 55 per cent of the cases. Pathogenic *E. coli*, on the other hand, was isolated from 1 day old feces in 72 per cent of the cases, from 3 days old feces in 58 per cent, from 5 days old feces in 48 per cent, and from 7 days old feces in 51 per cent of the cases. Apparently, the drying of feces causes a higher mortality of *E. coli*

Table I. The dried filter paper technique used for preserving pathogenic *E. coli*

	1 day old feces		*3 days old feces*		*5 days old feces*		*7 days old feces*	
Serotype	*No. examined*	*No. positive*	*No. examined*	*No. positive*	*No. examined*	*No. positive*	*No. examined*	*No. positive*
0111 : B4 : H2	103	73	69	55	55	38	46	44
086 : B6 : —	25	18	18	15	14	11	10	7
0126 : B16 : H2	22	19	18	17	14	14	10	7
0125 : B15 : H21	6	3	3	2	1	1	1	1
0119 : B14 : H6	6	4	4	3	2	2	–	–
0142 : K86(B) : H6	9	6	6	5	5	3	1	1
055 : B5 : —	5	1	1	1	–	–	–	–
0127 : B8	10	10	10	7	6	3	2	2
0128 : B12 : —	1	1	–	–	–	–	–	–
Total	187	135	129	105	97	72	70	62

Table II. The dried filter paper technique compared with buffered glycerol saline used for preserving pathogenic *E. coli*

	1 day old feces		*3 days old feces*		*5 days old feces*		*7 days old feces*	
Technique	*No. examined*	*No. positive*	*No. examined*	*No. positive*	*No. examined*	*No. positive*	*No. examined*	*No. positive*
Dried filter paper	96	79	78	57	56	44	32	22
Buffered glycerol saline	96	91	88	77	78	63	60	39

than of Salmonella or Shigella, a phenomenon which was also noticed in previous studies,[5, 6] and which often resulted in relatively better isolation of the latter organisms from feces. The mortality among pathogenic *E. coli* is, apparently, highest in the first 3 days and becomes lower between the third and seventh days after drying.

The use of buffered glycerol saline gives somewhat better results than the dried filter paper technique. The dried filter paper method is very simple, however, and can be utilized under the most primitive conditions. The low mailing cost makes it possible to send specimens to distant typing centers, whereas buffered glycerol saline tubes are costly to send by air. We, therefore, recommend the use of the dried filter paper technique for preserving pathogenic *E. coli* only when the fecal specimen has to be sent by air over long distances. Pathogenic *E. coli* can be recovered in about 50 per cent of the positive cases when the mailing time is between 3 and 7 days. A shorter mailing time would ensure better results. Varela[13] has also obtained good results with the dried filter paper technique employed for preserving pathogenic *E. coli,* Shigella, and Salmonella.

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MEDICAL PROGRESS

Extracellular volume: its structure and measurement and the influence of age and disease

Donald B. Cheek, M.D., D.Sc.*

MELBOURNE, AUSTRALIA

IT IS the purpose of this paper to discuss the structure, measurement, and interpretation of extracellular volume, its changes with age and disease, and particularly its pattern in early life. In pediatrics, disturbance in volume is frequent due to the high incidence of diarrhea, malnutrition, and congenital defects of the pylorus, adrenal, renal tubule, and central nervous system. Moreover, while the extracellular volume of the infant is large on a weight basis (as compared with the adult), this volume is strikingly low in relation to some physiologic needs, such as oxygen consumption, insensible perspiration, and cardiac rate. Consequently, when subjected to stress, the infant is frequently unable to maintain homeostasis.

The measurement of extracellular volume has helped to elucidate the nature of change in body composition during disease. For example, in tuberculous conditions of a generalized type or in tuberculous meningitis hypotonic expansion of extracellular fluid volume occurs with loss of cell water.[1, 2] A low plasma sodium concentration is present, but sodium depletion in the body is not necessarily present. This biochemical lesion is of importance and can, if exposed, contribute to the establishment of a correct diagnosis.[2]

In most pediatric centers there are means for determining changes in electrolyte concentration in the plasma. The detection of change in volume, however, is not so convenient, and usually values for plasma sodium or chloride concentrations represent concentrations in an unmeasured volume. In point of fact, the volume of distribution of chloride follows approximately what can be thought of as the extracellular fluids, whereas sodium distribution follows closely total body water.[3] Since the total amount of sodium or chloride is equal to the volume of their distribution multiplied by their respective concentration, it is clear that an assessment of the amount of sodium or chloride loss cannot be made unless information on volume is also available.

A rapid and convenient method for the appraisal of changes in fluid volume in pediatric patients would be very useful. The clinical appraisal of dehydration is not always

*Address, Royal Children's Hospital, Pelham Street, Carlton, Melbourne, N.3, Vic., Australia.

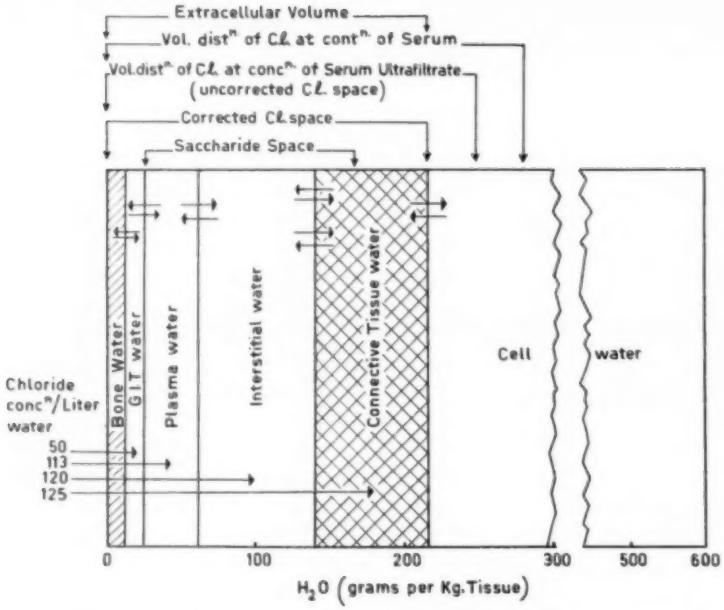

Fig. 1. The relative size of the subcompartments that make up extracellular volume is shown. The diagram is based on experimental data from the rat.[8] Such subdivision is probably similar for all mammals.

certain. The establishment of definite and sudden loss of weight is of considerable importance, while the loss of tissue turgor and elasticity of the skin is indicative of a greater loss of sodium than of water (hypotonic dehydration). No such noticeable change of skin texture may be apparent in the infant who has undergone a severe water loss per se,[4, 5] and the previous loss of weight may not be in the available information of the case history. The demonstration of a coincidental hypernatremia may be the first presumptive evidence of a severe loss of body water. The obese child and the malnourished infant both present problems when the clinical assessment of dehydration is necessary. Insofar as change in blood volume is frequently (but not always) accompanied by change in extracellular volume in the same direction, the hematocrit, in the absence of anemia, is some guide to change in volume. Likewise, the red blood cells act as osmometers, and measurement of mean corpuscular volume is a guide to the status of cell volume. It would seem, however, that a method for the rapid and easy appraisal of the volume of extracellular fluid should have a place in clinical diagnostic procedures.

DEFINITION AND MEASUREMENT OF EXTRACELLULAR VOLUME

Extracellular volume is an important parameter of the body. Anatomically, this phase of body tissues defines the volume of fluid that surrounds and bathes the cells. It can be thought of as including 3 major components, plasma water, interstitial water (e.g., lymphatic fluid), and connective tissue water (including water in bone and cartilage), which collectively make up about 20 per cent of the body weight in the mature animal. The moiety of fluid in the central nervous system, the eye, the gastrointestinal tract, the pericardium, pleura, and joints has been called "transcellular fluid"[6] (meaning not a simple transudate), and this fluid is part of the extracellular phase. Of these transcellular fluids, the only one of size is the

fluid within the gastrointestinal tract, which makes up 3 per cent of total water in the dog[7] and about 2.4 per cent in the rat.[8] Clearly, almost all the extracellular fluid resides in the plasma water, the interstitial water, and the water present in collagen, cartilage, and bone tissues. The relative size of the major components of extracellular volume and of the larger transcellular fluid of the body is of importance (Fig. 1). Unfortunately, no such data exist for the human being. However, studies on body analysis in the rat weighing 220 grams[8] allow certain estimates to be made. Such a rat possesses a total body collagen content of 11.9 Gm., while 1.4 ml. of water are associated with each gram of the connective tissue (tendon). Hence 16.6 ml. of water are present, if tendon water represents the over-all water content of connective tissue, as certain studies indicate.[9] The concentration of bone water in a rat weighing 220 grams is about 23 ml. per 100 Gm. of dried bone,[10] and from the ratio $\frac{\text{Bone } H_2O \text{ concentration}}{\text{Bone calcium concentration}}$ and the known total body calcium content of a rat weighing 220 grams it can be estimated that 2.6 ml. of H_2O are associated with bone. From available data on the blood volume of the rat,[11] it can be calculated that plasma water is 7.9 ml. By experiment it was found that 3.6 ml. of fluid is present in the gastrointestinal tract.[8] All these fluids make up a total volume of 30.7 ml. By experiment it was found that the total extracellular volume in the rat weighing 220 grams is in the region of 48 ml. (The reason for believing that this value is close to true extracellular volume will be discussed presently.) For interstitial and lymphatic fluid, the above data predict a value of 48.0 – 30.7 = 17.3 ml. (Table I).

Such measurements, although arrived at indirectly, are based on experimental work. They suggest that for the mature rat one-third of extracellular water is derived from water in connective tissue, one-third from interstitial water, and about one-third from plasma, bone, and gastrointestinal fluid. It should be pointed out that the above estimates do not agree with the values put forward for man by Edelman and Liebman.[12] These authors estimate that connective tissue water is only 45 ml. per kilogram. Since saccharides (which will be discussed presently) penetrate 25 per cent of connective tissue water in a short time, they contend that this fraction of connective tissue water belongs to the interstitial fluid, giving a total, for that subcompartment, of 120 ml. per kilogram. They based their calculations for body water in collagen on data available for the guinea pig.[13] However, their approach is to deny anatomic boundaries and any portioning of extracellular fluid should be morphologic as well as physiologic. The fact that a large molecule like inulin is quick to penetrate only a fraction of connective tissue water has little to do with the fact that all water in most connective tissue moves rapidly and is quickly exchangeable.

While the majority of the fluids comprising the total extracellular fluid are simple transudates, the over-all picture is that of a group of nonidentical fluids with a high concentration of chloride and a low concentration of potassium situated outside the tissue cells of the body. A priori, it must be emphasized that no single substance when injected intc the body distributes itself over the vol-

Table I. Constituents of extracellular fluid volume (48 ml.) of a rat weighing 220 grams

Major components		
1. (a) Connective tissue water	16.6 ml.	75.7 ml. per kilogram
(b) Bone water	2.6 ml.	11.8 ml. per kilogram
2. Plasma water	7.9 ml.	36.0 ml. per kilogram
3. Interstitial and lymphatic fluid	17.3 ml.	78.8 ml. per kilogram
Chief transcellular fluid		
Gastrointestinal fluid	3.6 ml.	16.3 ml. per kilogram
Total		218.6 ml. per kilogram

ume of these fluids with exactness, nor is it likely that such a substance will be found. However, the volume of distribution of chloride possessing a concentration equal to a plasma ultrafiltrate (the chloride space) does satisfy the requirements in an approximate manner. Moreover, if the chloride space is corrected for the amount of chloride that is not extracellular e.g., chloride in red blood cells, it is possible to define a space that is probably close to the true extracellular volume. The truth of the preceding statement rests squarely on the evidence that only a small fraction of chloride is intracellular. This evidence needs discussion.

As early as 1901 Vandergrift and Gies[14] drew attention to the large amount of chloride in connective tissue. In 1934 Fenn, Cobb, and Marsh[15] alluded to the "chloride space" of muscle tissue. The chloride space was defined as the volume of distribution of chloride in a separate tissue or in the whole body. It represented the amount of chloride present divided by the concentration of chloride in a serum ultrafiltrate (usually 120 mEq. per liter). Harrison, Darrow, and Yannet[16] were the first to use the chloride space in 1936 to partition extracellular volume in the whole animal. In 1937 Hastings and Eichelberger[17] concluded from tissue analyses that chloride was predominantly though not exclusively extracellular. In 1939 Manery and Hastings[18] demonstrated an inverse relationship between chloride content and potassium content in a wide variety of mammalian tissues. Since potassium is representative of the intracellular compartment and the total water of tissues is reasonably uniform, their finding suggested a predominantly extracellular position for chloride. The greater the intracellular compartment (potassium) the less was the extracellular (chloride). Manery, Danielson, and Hastings[9] predicted that the extracellular phase in different tissues was mostly a connective tissue phase diluted with an ultrafiltrate of plasma. The ratio of $\frac{\text{tissue sodium}}{\text{tissue chloride}}$ for tendon was similar to that in the plasma ultrafiltrate of many tissues.[19] Later studies[19, 20] using isotopes of chloride demonstrated a rapid equilibrium of Cl^{38} with stable chloride in tissues. The work of Amberson and associates[21] and Hiatt[22] demonstrated that, if the chloride of the body were replaced with sulfate or nitrate, the tissue chloride fell commensurately with serum chloride. Muscle biopsies placed in isotonic sucrose rapidly lost all their chloride. The chloride content of muscle was directly proportional to the chloride concentration of a solution in which a specimen of muscle was immersed. The volume of distribution of sulfate, thiocyanate, iodide, bromide, hemoglobin, and indigo carmine in muscle all closely approximated the chloride space of muscle.[23] Cotlove[24] studied the position of chloride in muscle tissue of the rat by the prolonged and constant infusion of inulin and sucrose, with subsequent analysis of the muscle for saccharide content. These saccharides did not penetrate tissue cells and the analysis of tissue for inulin excluded any errors that arose from metabolism of the saccharide. Cotlove found that the saccharide space of muscle was equal to the chloride space. In other words, no chloride was found within the muscle cell. Similar and equally important data were obtained by Nichols and colleagues[25] concerning muscle and tendon. They showed that inulin and thiosulfate did not penetrate the entire water content of connective tissue over a period of 6 hours, and hence did not measure extracellular fluid within that time. If, however, correction was made for the amount of water in the tendon not penetrated by inulin, agreement was reached between the chloride, inulin, and thiosulfate spaces.

Cheek, West, and Golden[8] studied the location of sodium and chloride in the mature 220-gram rat (referred to previously). Whole body analyses were carried out for all electrolytes, together with analyses of individual tissues. The observations of Cotlove[24] for muscle were extended to viscera. The constant and prolonged infusion of inulin was used, together with subsequent analysis of viscera for inulin content. Once again it was found that the inulin and chloride spaces of

viscera were almost equal. There was evidence that a minute fraction of body chloride was intracellular in liver cells. Other studies concerning liver also underline a predominantly extracellular position for chloride in liver tissue.[26] While gastric mucosa and kidney contain some intracellular chloride, in terms of total body chloride such amounts are small. In our studies it was not possible to analyze the central nervous system, but the brain and spinal cord contain only 2 per cent of body chloride[27] and it is unlikely that the majority of this chloride is intracellular. Since muscle makes up 50 per cent of the body weight, and the viscera another large part, it should be clear that no large amount of chloride is intracellular in the body. Of the remaining tissues, connective tissue represents a pure form of the extracellular phase,[19, 25] while the volume of water in the bone agrees with estimations of the chloride space of bone.[10] Indeed, the problem would seem to be to locate intracellular chloride.

Several studies are available which show that the dog has a total body chloride of 33 to 35 mEq. per kilogram.[16, 28-31] Swan, Madisso, and Pitts[31] found that in nephrectomized dogs, 6 hours after injection, radio sulfate, thiosulfate, and mannitol all gave equal volumes of distribution. They measured the total body chloride with Cl^{36} and after correcting for red cell chloride found that some 6 mEq. per kilogram of chloride (17 per cent of body chloride) was outside the space they had measured. At about the same time Nichols and associates[25] showed that this sulfate only penetrates 76 per cent of connective tissue water within 6 hours in the nephrectomized dog and does not distribute over the whole extracellular volume. Assuming that the dog has an amount of collagen water similar to that of the rat per unit of weight (76 ml. per kilogram), this would mean that 20 ml. per kilogram of extracellular water were not measured in the study by Swan and co-workers. This water contains 2.4 mEq. per kilogram of chloride. Also, transcellular chloride present in the gastrointestinal fluids should be allowed for in their considerations. Cizek[7] has shown that gastrointestinal fluid is also about 20 ml. per kilogram in the dog and should account for 1 mEq. per kilogram of body chloride. Therefore, at best, probably no more than 2.6 mEq. of chloride per kilogram out of the 6 mEq. can be considered as possibly intracellular in the dog. This amount, added to red cell chloride, predicts that 13 per cent or less of body chloride is located intracellularly in the dog.

In the studies on the rat weighing 220 grams[8] it was found that 90 per cent of total body chloride was extracellular, while the majority of nonextracellular chloride was present in red blood cells (6 per cent) or in visceral cells (1.8 per cent). The corrected chloride space of the whole rat was 47.4 ml. From analyses of bone and the ratio of bone sodium to bone calcium, and on the assumption that all calcium in the body is in bone, it was possible to calculate the body content of nonextracellular bone sodium. When the volume of distribution of sodium in the rat was corrected for bone sodium and for sodium in muscle, visceral, and red blood cells, an extracellular volume of 47.9 ml. was obtained for the rat. This close agreement is significant, since 21 per cent of sodium is in bone and the locations of nonextracellular chloride and of sodium are different. Calculation of intracellular volume and of net cell potassium and magnesium concentration revealed intracellular cation concentrations similar to those known to be present in muscle cells, the major tissue cells of the body.

These previous considerations lend credence to the view that in the rat, the dog, and probably in the human some 10 to 13 per cent of chloride is intracellular. In a recent appraisal of the distribution of chloride in man by Edelman and Liebman,[12] it was concluded that 12.4 per cent of chloride was intracellular.

Therefore the correction of the chloride space in the whole body by a factor of 10 per cent should approximate the true extracellular volume. The chloride space when corrected gives the most meaningful appraisal of extracellular volume. During se-

vere disease, with disorganization of body composition, the same confidence cannot be expressed.[32]

The chloride space can be measured at the bedside with substances that follow the distribution of chloride in the body very closely. Such agents are stable bromide, Br^{82}, or isotopes of chloride.[33-37] Perhaps stable bromide is the most useful. Only small amounts are needed for injection (enough to raise the blood level to a concentration of 1 to 2 mEq. per liter so that osmotic equilibrium is not disturbed. Bromide is not metabolized in the body, is only slowly excreted,[38, 39] and rapidly reaches equilibrium in the presence of edema.[38] About 3 ml. per kilogram of a 2 per cent solution of sodium bromide orally, intravenously, or subcutaneously will suffice to give a satisfactory blood concentration in the infant or child. After 2½ hours the distribution of bromide reaches a stable level[27, 38] and at most only increases by about 2 per cent from 3 to 24 hours[27] and thereafter may remain constant for several days, particularly if the sodium chloride intake is restricted or if the patient has difficulty in excreting chloride and sodium.[38] Bromide and chloride distribute in a similar manner in all tissues[33-37] with the exception of the thyroid and central nervous system. In the rat, after 3 hours of equilibration, the exchangeable chloride as measured by stable bromide approximated the total body chloride as measured by body analysis.[33] Isotopes of chloride and bromide are of equal value in determination of the corrected chloride space. A correction factor of 10 per cent is applied to the bromide or chloride space to allow for nonextracellular anion.

The method of determination of plasma bromide concentration in our hands has been by microdiffusion,[33] using the diffusion units of Obrink.[40] Alternatively, a reliable method has been published by Hunter.[41] Both methods are time-consuming. A polarographic method by Jones and Terry[42] should be quicker and can be done on 0.1 ml. of serum. Wolf and Eadie[39] removed the difficulties from the early gold chloride method, and Finley and Hare[43] have demonstrated its value in the estimation of the bromide space.

Injected thiocyanate also approximates the volume of distribution of chloride[44, 45] but this ion is bound to a nondiffusible component in the plasma, mainly albumin.[46] Hence a correction factor must be applied for this phenomenon and also for the entrance of the ion into red blood cells. It is not known how much thiocyanate is bound to extravascular albumin or whether this ion penetrates cells other than red blood cells. However, agreement has been obtained between the corrected chloride space and the corrected thiocyanate space.[44]

The distribution of radiosulfate in the body has been used and is used as a measure of extracellular volume[47] but incomplete distribution is found and radiosulfate space increases with time. This space in muscle is 20 per cent less than the chloride space[48] so that the volume of distribution of sulfate departs from the chloride space and measures a volume that may be useful in terms of comparison of health with disease, but it does not approximate true extracellular volume. The same criticism can be leveled at thiosulfate, which does not penetrate connective tissue effectively. It is metabolized in the body.[25]

Much work has been done on the use of saccharides to measure extracellular volume. Except for conditions to be mentioned with regard to isolated tissues, however, these substances are of little value in measuring extracellular volume in the whole body. Connective tissue water is an integral part of extracellular fluid, making up perhaps as much as one-third of the total volume, yet inulin and sucrose, for example, do not penetrate these tissues rapidly[25] and not completely over a 6-hour period. Prolonged infusion of inulin is necessary for penetration of connective tissues. Trouble is encountered because inulin is slowly metabolized by tissues.[49, 50, 51] Hence prolonged infusion makes necessary the removal of the tissues under study for direct analysis of inulin content so as to obviate errors due to metabolism; this technique could not be applied clinically. The inulin space of liver cells is greater than

the chloride or sodium space, which suggests that inulin enters liver cells.[8] Inulin penetrates the chloride space of viscera and muscle rapidly[8, 52] but in tissues like the skin, where collagen is rich, a prolonged infusion technique is necessary and even then complete penetration would probably never be reached because of metabolism.[25] Thus the infusion of inulin, sucrose, or mannitol into the whole body[53, 54] results in similar volumes of distribution, but much less than the extracellular volume or corrected chloride space, and these saccharines do not penetrate gastrointestinal fluids. Calculation of net cell concentration of cation[8] in the noninulin fraction of total body water gives values for intracellular potassium concentration that are incorrectly low. In earlier days it was erroneously thought that saccharides measured the entire extracellular phase, and hence it was falsely deduced that large amounts of chloride (20 to 40 per cent) in the noninulin space were intracellular.[55, 56, 57] The chloride space was considered by some to be a poor measure of extracellular volume. This is not so.

NORMAL VALUES FOR EXTRACELLULAR VOLUME

The mean value for the corrected bromide space obtained for 20 normal neonatal infants by Fink and Cheek[58] was 358 ± 6.5 ml.* per kilogram of body weight. The infants were from 5 to 15 hours old. No variation in volume was found between the sexes. The total chloride was estimated to be 48 mEq. per kilogram of body weight. Forbes and co-workers,[27] using Br^{82} and a 24-hour period of equilibration with correction for urinary bromide excretion, found that the total chloride was 51 mEq. per kilogram in the newborn period. Their value is probably more correct because they used a 24-hour bromide equilibration, where the volume of distribution of bromide is said to be 2 to 3 per cent larger than at 3 hours. Also, they corrected for urinary loss of bromide over this extended period. Darrow and Hellerstein,[59] from data on body analysis in the literature, gave a value of 52 mEq. per kilogram for body chloride at this period, while Shohl[60] placed the figure at 50 mEq. per kilogram.

Finley and Hare[43] estimated the volume of distribution of bromide in 13 infants on the second day of life. If their data are corrected for nonextracellular bromide and if the serum bromide concentration is corrected for Donnan equilibrium and for serum water, a mean value of 368 ml./Kg. ± 4.2 ml.* is obtained. It would appear that there is little change in extracellular volume during the first 48 hours of life. Since weight loss begins shortly after birth, it is possible that this early weight loss of the normal infant is mainly intracellular water loss.

From a few weeks of age to 1 year of age, there is a more rapid and progressive loss of extracellular volume in proportion to body weight. In 20 infants[61] from the early weeks of life to 9 kilograms (1 year), the corrected bromide space in liters is given by:

$$\text{Corrected bromide space} = \frac{27.63 \text{ weight} + 49.5}{[Cl]_e} \pm 0.08 \text{ L.}$$

(where weight = weight in kilograms and $[Cl]_e$ is the concentration of chloride per liter of water in a serum ultrafiltrate).

From 1 year of age to late childhood[61] (30 children weighing 10 to 30 kilograms), the corrected bromide space in liters is given by:

$$\text{Corrected bromide space} = \frac{28.67 \text{ weight} + 35.5}{[Cl]_e} \pm 0.09 \text{ L.}$$

These data are in agreement with those of Forbes and associates[27] and Macaulay.[44] Also, Finley and Hare[43] obtained almost identical data in 19 children.

When surface area was plotted against the volume of distribution of bromide[43] on a log–log grid, the equation for the line was calculated to be

$$y = 0.6\ x^{1.2}$$

where y = volume of distribution of bromide $\left(\frac{\text{bromide injected}}{\text{serum Br concentration}}\right)$ and x =

*Standard error.

*Standard error.

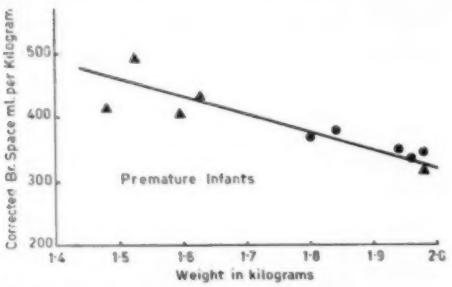

Fig. 2. The corrected bromide space of premature infants is plotted against body weight. Data of Finley and Hare[43] are shown by black dots (infants 2 to 18 days old) while the triangles represent previously unpublished data for infants 25 to 30 days old. Extracellular volume would seem to be more closely related to weight than to age—the smaller the weight, the larger the extracellular volume.

surface area. The constants 0.6 and 1.2 were found to be identical with those which can be calculated from the data for children presented above.[61] By combining all these data Finley and Hare constructed a nomogram for the rapid assessment of the volume of distribution of bromide. To calculate the corrected bromide or chloride space from their nomogram, it is necessary to correct for the concentration of bromide in a serum ultrafiltrate and to deduct 10 per cent of the injected bromide (to correct for nonextracellular ion). In other words, it is necessary to multiply the value from the nomogram by 0.75.

In adult life the corrected bromide space is equal to about 22 per cent of body weight[38]; this value has been confirmed by Reid and co-workers[62] and by Ljunggren and others.[63] Prior to birth, values for total body chloride of 50 to 80 mEq. per kilogram have been found,[27] and during the greater part of fetal life extracellular volume makes up, no doubt, the largest phase of total body water.

In Fig. 2 data concerning the corrected bromide space of 10 premature infants has been plotted against weight. The position of the points emphasizes that the smaller premature infants have a higher extracellular volume per unit of weight than those approaching normal birth weight.

The values for extracellular volume mentioned above serve as a base line for the investigation of disease, for detection of extracellular sodium loss, for the measurement of edema, and for the detection of malnutrition or changes in cell composition. Data are available by other workers who have used the volume of distribution of other agents to measure extracellular volume[64-74] and the limitations of these agents have been discussed.

THE RELATION OF EXTRACELLULAR WATER TO TOTAL WATER

Since extracellular water is intimately associated with total body water, it is important to define the relationship of these to each other during growth. Adequate data on the deuterium or antipyrine space in infants and children are now available.[74-78] The same can be said for the corrected bromide space,[27, 43, 58, 61] except for the period of 3 days to 28 days of life. In Fig. 3 it can be seen that during the first 2 days of life the mean value for total water is 783 ml. per kilogram, while the corrected bromide space makes up 46 per cent of the total body water. By the end of the first month of life total water begins to fall. Limited data on only 4 infants suggest that the fall in extracellular volume is delayed. This point needs further elucidation. Assuming these 4 values to be representative, extracellular water is still 48 per cent of total water. At the end of the first year of life total water falls to 642 ml. per kilogram and extracellular water to 302 ml. per kilogram. However, extracellular volume is still 47 per cent of total body water. It seems that the fall in body water and extracellular water is proportionate during the first year of life. During the second year values for total water begin to mimic those of the adult and older child. Here extracellular water makes up 41 per cent of the total body water. During the second year of life it would seem that the child reaches "chemical maturity"[79] and begins to resem-

ble the adult with respect to body water, chloride, and extracellular volume. With increasing growth there is a relative increase in cellular water.[80]

The expression of extracellular water as a fraction of total body water is useful. In many disease states in the absence of edema total water remains unchanged.[81] This is also so in obesity. Hence weight or even surface area at times fails to be a suitable standard of reference for extracellular volume. Change in the absolute amount for age and in the normal relationship of extracellular volume to total body water will predict a state of abnormal composition more reliably.

EXTRACELLULAR VOLUME AND THE DIFFERENTIAL GROWTH EQUATION

Huxley[82] showed that the growth of an organ or limb in the body was related to the growth of the rest of the body, in accordance with differential growth equation: $y = bx^k$ where y = weight of the body, x the weight of the organ, and b and k are constants. Taking logarithms, this equation is that of a straight line $\log y = k \log x + \log b$. This

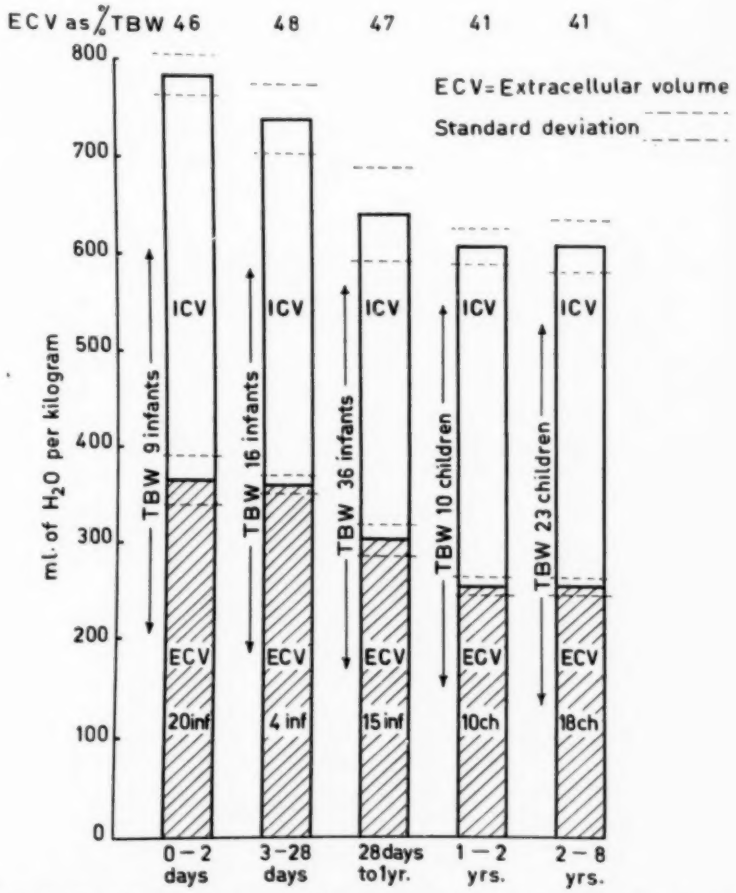

Fig. 3. This diagram illustrates the fraction of total body water (deuterium space) made up by extracellular volume (corrected bromide space) at various age levels.

equation also holds when total water or electrolytes are substituted for the weight of an organ as has been discussed by Forbes.[27, 83] He concluded that chemical growth is a regular and systematic process during life. Friis-Hansen[74] plotted available data for total water on a double logarithmic scale and concluded that there was a definite break in the linear relationship between 3 and 10 kilograms of body weight. A new straight line was then commenced.

In Fig. 4 the corrected bromide space for 20 newborn infants on the first day of life,[58] for 13 infants on the second day of life[43] and for older infants up to 10 kilograms[61] has been plotted against body weight on a double logarithmic scale. Clearly one line ends and another begins at about 5 kilograms of body weight. It can be argued that the differential growth equation only concerns total water or electrolyte, but since extracellular volume is a function of total chloride the present approach would seem justifiable. Forbes and co-authors,[27] by plotting data fo total body chloride for the fetus, for new born and older infants, and for adults, cam to the conclusion that a second line fo total chloride begins in the postnatal area The present data pinpoint this area o change.

Regression equations have been calculated for the total body chloride[27] and the corrected bromide space can be calculated from these. It is of considerable interest that the total chloride (and extracellular water) appears to have a smooth mathematical relationship with weight from midfetal life up until some weeks following birth before changing to a new relationship which lasts during the rest of life. The slopes of these lines, however, are similar[27, 83] and also show striking similarity to the slopes from data for the rat and other mammals.[83] This suggests that there is a basic plan to chemical structure during growth, as suggested by Needham.[84]

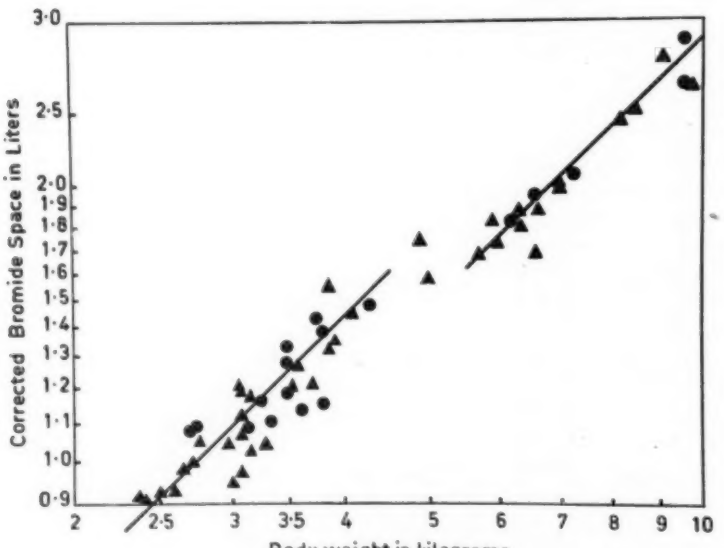

Fig. 4. On a log-log grid the corrected bromide space from birth to 1 year has been plotted against body weight. Note that two separate but parallel lines are obtained showing that a new mathematical relationship between the two components begins at about 6 weeks of life. ▲ = data of Cheek[61] and Fink and Cheek,[58] while ● = data of Finley and Hare.[43]

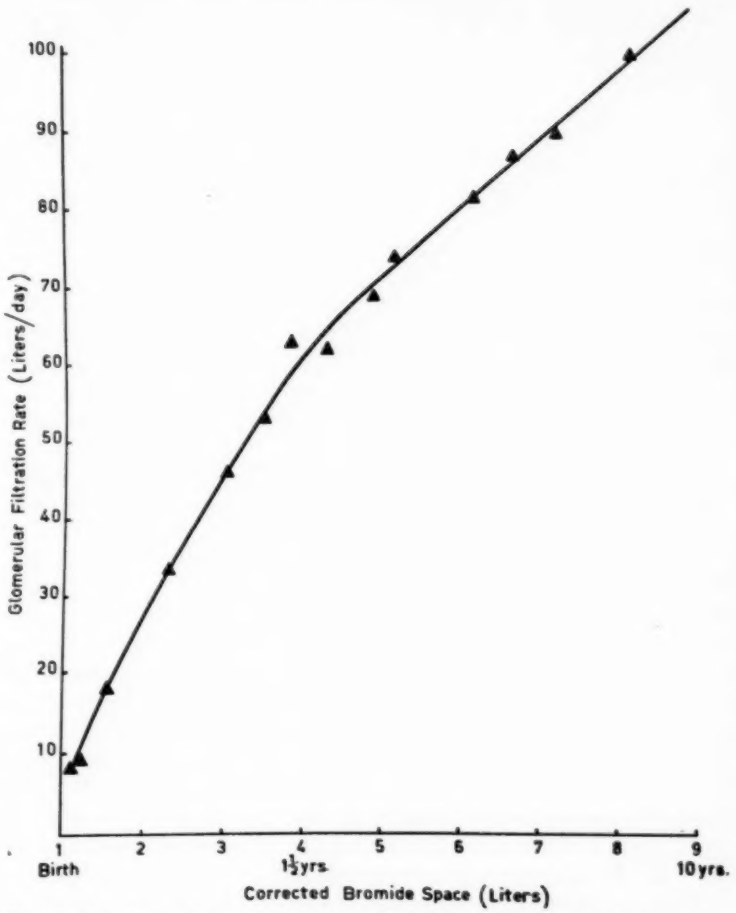

Fig. 5. This figure shows the definite relationship between extracellular volume and glomerular filtration rate per day. The latter values have been taken from the data of Winberg[86] and have been plotted against the corrected bromide space, which was calculated from the surface area of each subject by the formula of Finley and Hare.[43]

GLOMERULAR FILTRATION RATE AND EXTRACELLULAR VOLUME

Total body water and extracellular water are important parameters of the body. Body water maintains a constancy of volume and at the same time a dynamic equilibrium. One of the most dynamic aspects is the constant filtration of fluid through the glomerulus. The measurement of filtration rate in terms of body surface area has not proved very satisfactory in pediatrics. When compared on the basis of surface area, renal function in children under 2 years is seemingly lower than that of adults. McCance and Widdowson[85] considered that total water was more appropriate as the standard of reference. However, extracellular fluid is the medium with which the kidney works, as emphasized by Friis-Hansen.[75]

In Fig. 5 the data of Winberg[86] for the glomerular filtration rate obtained by estimation of endogenous creatinine clearance have been plotted against the corrected bromide space. The corrected bromide space has been

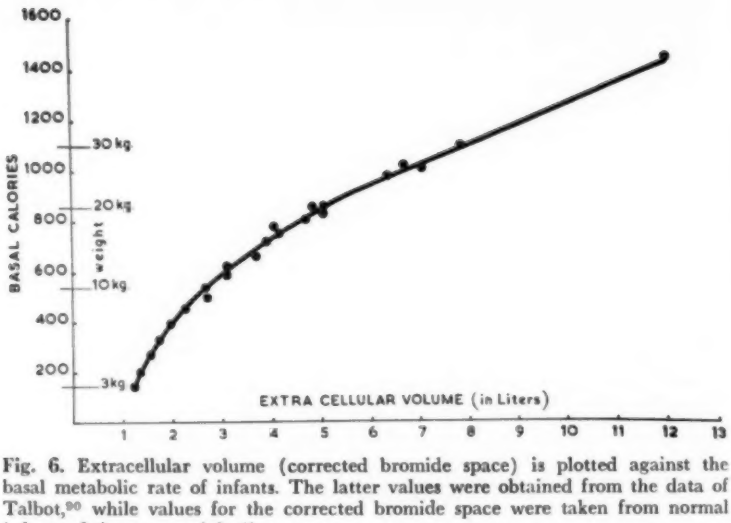

Fig. 6. Extracellular volume (corrected bromide space) is plotted against the basal metabolic rate of infants. The latter values were obtained from the data of Talbot,[90] while values for the corrected bromide space were taken from normal infants of the same weight.[61]

calculated from the surface area of each "renal" subject with the use of the formula of Finley and Hare[43] and the factor of 0.75 mentioned previously. The good correlation between these entities is apparent. There is a slight curvilinear relationship from the early days of life to about 1½ years of age, after which time a straight-line relationship pertains. Theoretically, the extracellular volume passes through the glomerular membrane 8 times per 24 hours in the early days of life, and this rate increases gradually to 16 times per 24 hours at about 2 years, after which this value falls gradually to 12 at 10 years of age. Hence, if we think in terms of volume exchange, the turnover of extracellular fluid through the glomerular membrane is greater and renal function more active in the child than the adult. It must be remembered that metabolism is higher in the infant and child in terms of unit weight, and the need for such turnover is apparent. The line shown in Fig. 5 should serve as a means of assessing abnormal states of renal function.

METABOLISM AND EXTRACELLULAR VOLUME

For more than a century men have sought to find a close relationship between basal metabolic rate, age, sex, size, and other dimensions. Such possible correlations may imply physiologic relationships that do not exist. Crandall and Anderson[87] found that the thiocyanate space related better to surface area than to weight, and they suggested a good relationship between metabolic activity in adults and volume. Dahlstrom[88] subsequently showed that the thiocyanate space closely correlated with basal metabolic rate, regardless of age or sex. He suggested that the relationship was due to the osmotic contribution of metabolites to extracellular fluid. His demonstration was subsequently confirmed for adults by Wedgwood and colleagues,[89] who have also used the thiocyanate space. It was apparent from statistical analyses that there was an excellent relationship between extracellular volume or interstitial volume in man and metabolic rate. Indeed, other correlations were not as good (for example, total water or surface area). Other things being equal, if metabolic rate or sympathetic activity is higher in one infant than in another, then extracellular volume should be slightly larger in the one with the higher rate.

In Fig. 6 the corrected bromide space of infants and children of a definite weight is

plotted against the basal metabolic rate of other normal children of corresponding weights.[90] It is clear from the graph that in early infancy there is not a linear relationship between the two measurements. In fact there is actually less extracellular water available for every 100 basal calories consumed by the infant than is the case for the adult or older child. If, in addition, we realize that, during infection or stress, the pulse rate, insensible water loss, and oxygen consumption of the infant may be double that of the adult, the limitations in the face of "stress" become clear. In the words of Kerpel-Fronius,[91] "When put under stress, however, the fragility of the whole system which maintains body fluid homeostasis is exposed." Water loss, salt loss, severe infections, interference with hemodynamics, with adrenal or renal function, all produce illness or death more quickly in the infant.

Consider for a moment the condition of acrodynia. Here stress plays an important role.[92] The physiopathology of the disease[93] is such that renal salt loss occurs, together with large skin water losses. There is reduction of extracellular volume and tendency to hypotonic dehydration. Persistent tachycardia is present, with potentiation of metabolism of epinephrine, elevation of basal metabolic rate, and sympathetic adrenal cortical imbalance.[94-95] No wonder sudden death with peripheral vascular collapse, occurring in a matter of minutes, was seen repeatedly in the days when this disease was common.

Kerpel-Fronius and associates[96] found that the diminution of oxygen requirements brought about by a lowered metabolism protects against stagnating anoxia. Such anoxia is found in the circulation during dehydration. Under some circumstances, then, the infant may be more resistant to dehydration when under conditions of reduced metabolism, as in starvation. Here the reserves of extracellular volume will be more expendable. However, it must not be thought that starvation is beneficial for any long period in the dehydrated infant. Indeed, as Talbot and co-workers[97] have shown, the restriction of food is reasonable only for a week. The adult can withstand deprivation for 4 weeks. When infants are deprived of water, illness will eventuate in a fifth of the time that would be needed for the adult.

ABNORMALITIES OF EXTRACELLULAR VOLUME IN THE EARLY MONTHS OF LIFE

Up to this point the discussion has dealt with certain anatomic, chemical, and physiologic aspects of extracellular volume. It is pertinent to discuss some pediatric conditions involving an abnormal change in extracellular volume.

While the progress of work has included studies of extracellular volume in normal infants in the early days of life,[43, 58, 65] little or no measurements have been made concerning abnormal situations. Edema is frequently seen in the neonatal period, particularly in infants with respiratory distress and anoxia. Smull[98] measured the bromide space of such infants and reported values of 550 ml. per kilogram. The reason for this expansion of extracellular water is not apparent. One has wondered what role, if any, steroids play at this period.* To elucidate whether a large circulating steroid concentration in the newborn would expand extracellular volume, hydrocortisone and desoxycorticosterone were injected in large doses and measurements were made with bromide.[58] No significant expansion of volume was found 6 hours later. It would appear that sodium-retaining steroids are physiologically adequate at this period of life.[99]

McCance,[100] in a consideration of the mechanisms of the newborn, draws attention to the fact that a small increase in the concentration of sodium chloride in the milk intake ensures a large load of sodium because of the relatively high fluid intake of the infant at this period. Edema may eventuate with hypertonic expansion of the extracellular fluid. At the same time, there is a fall in serum urea and presumably less tissue break-

*Work in progress shows that aldosterone in doses as small as 0.0001 μg will produce Na, Cl, K, and water loss in 35- to 40-day-old mice, under saline loading. In older animals K loss is the conspicuous finding.

down. McCance is inclined to the view that, with the expansion of extracellular fluid, there is activation of some mechanism, perhaps acting through the adrenal gland that reduces tissue breakdown. The rapid growth of the premature and newborn infant would be related to the relatively greater volume of extracellular fluid.

One infant, in the author's experience became edematous with abnormal weight increase when given cow's milk. The bromide space was 500 ml. per kilogram. The introduction of milk with a low sodium content removed the edema. This situation persisted for some weeks, but the subsequent course was uneventful. It is possible that the relatively high content of sodium in cow's milk relative to human milk may be responsible for the occurrence of edema in some infants. At the same time, as pointed out by McCance,[100] the substitution of water for milk in the newborn animal will also lead to excessive gains in weight and hypotonic expansion of body fluids.

Another infant that presented early in life to the present author at the Royal Children's Hospital, Melbourne, was found to have a sodium-wasting syndrome[101] not related to adrenal hyperplasia or to lack of production of adrenal hormones. No cerebral or renal disease was detected. A reduction of extracellular volume was found with hypotonic dehydration. No correction of the volume deficit or hypotonicity was possible with desoxycorticosterone; only additions of sodium chloride to the diet were effective. It was thought that the syndrome was related to a failure of endogenous mineralocorticoid to act at the level of the renal tubule. The patient is at present a normal child of 5 years, but in early life exhibited all the clinical signs associated with adrenal insufficiency, with an abnormal distribution of water that is typical of sodium depletion.[101] Recently Donnell and colleagues[103] have brought forward equally strong evidence in another patient and they have demonstrated a high excretion of aldosterone in the face of dehydration and loss of salt.

In infants with adrenal hyperplasia, dehydration can also be remarkable, and likewise the loss of body sodium, which is accompanied by a lowered excretion of aldosterone.[99] In 1 patient with this syndrome it was found that the reduction of extracellular volume and of the intracellular volume were commensurate at a time when steroid and salt therapy was not being given. The pattern of volume loss may not resemble simple depletion of salt.[102] Problems of renal disease, diabetes insipidus, cystine storage disease, and renal acidosis all can lead to reduction of volume, either through increased sodium losses or losses of water; such conditions may present early in life.

Obstruction or inflammation of the gastrointestinal tract gives rise to vomiting or diarrhea or both. Gastroenteritis is still a

Table II. Water and electrolyte in muscle (mEq. or ml./100 Gm. fat-free dry solid)

	Water	*Chloride*	*Sodium*	*Potassium*	*Chloride space (ml.)*	*Intracellular water (ml.)*
3/12 years. Normal*	392	17.8	23.4	38.0	–	–
3/12 years. Fibrocystic disease of the pancreas	480	12.6	18.0	34.0	–	–
1½ years. Normal*	360	15.3	23.4	36.2	135	225
1½ years. Fibrocystic disease of the pancreas	464	13.6	20.2	47.0	118	346
2 years. Normal*	347	13.0	21.4	35.7	123	224
2 years. Fibrocystic disease of the pancreas	425	11.3	14.6	45.7	98.5	326
9 years. Normal*	347	13.0	21.4	35.7	–	–
9 years. Fibrocystic disease of the pancreas	245	9.7	13.0	34.5	–	–

*Data of Metcoff.[112]

very common disease, and the associated changes in volume deserve special mention. The condition of hypernatremia with gastroenteritis is of present interest. Attention was drawn to the greater loss of cellular water as opposed to extracellular volume in this condition.[5, 104] This is not always so.[105] Consider, for example, findings of a patient with a short history of diarrhea, a weight of 6.95 kilograms, a calculated weight loss of 900 grams (from previous weight) and a serum osmolality of 357 mOsm. per liter. The corrected bromide space was 1,630 ml. On the basis of preadmission weight, the normal space should have been 2,220 ml. It would appear that there was a loss of 310 ml. of cellular water and 590 ml. of extracellular.

Edema is sometimes seen during the course of treatment in gastroenteritis. Previous work[106] and that by other investigators[78] has shown that this is related to excessive sodium loading, a sodium load in excess of the deficits present. In the face of a loss of potassium, as in diarrhea, the inability to excrete sodium loads[107, 108] ensures expansion of the extracellular volume, edema, cell water subtraction, convulsions, and metabolic alkalosis. Such a situation was referred to previously[109] as the "post acidotic syndrome." Perhaps "post sodium repletion syndrome" would be a better name. In this condition hypernatremia is not the rule.[106] Hypernatremia may be more closely related to inappropriate adrenal stimulation.[105]

MALNUTRITION AND EXTRACELLULAR VOLUME

During the progress of work on body composition, a study was made on the effects of acute starvation on rats over a 1-week period.[109] The animals were provided with glucose, vitamins, and 20 mEq. per liter of salt in their drinking water. There was a 24 per cent loss of weight, 28 per cent loss of body potassium, a 20 per cent loss of fat-free dry solids, 18 per cent loss of water, and almost complete loss of fat. However, there was only a 6 per cent loss of salt. In most circumstances, total electrolyte yields a constant relationship with the fat-free dry solids of the body. However, when the total salt of the starved animals was compared with that of the normal rat (with the same weight of fat-free dry solid), it was found that the starved animals had a 13 per cent gain in total chloride and total sodium (in terms of the normal rat with the same weight of fat-free dry solid).

Starvation causes disorganization of body composition in contrast to the effects of high or low protein and electrolyte diets in rats.[110] Starvation causes a disproportionate increase in total sodium and total chloride and extracellular volume relative to fat-free dry solids. Since fat content of the body is inversely proportional to body water, the loss of fat yields an increase of water and chloride per unit of total body weight. When extracellular water of the patient is expressed in terms of lean body weight or as a percentage of total water, a clearer interpretation can be placed on measurements in many instances.

In fibrocystic disease of the pancreas, there is a loss of body fat. In 4 patients, ranging in age from 6 months to 4 years,[111] corrected bromide spaces of 35.6 to 28.3 per cent of body weight were found. On a body weight basis, there was expansion of extracellular volume. Consider the value of 280 ml. per kilogram for the 4-year-old patient with a weight of only 11.3 kilograms. At this age, the normal value is only slightly less (260 ml. per liter). Yet a relative expansion of the extracellular fluid volume should be prominent here, and, possibly with loss of fat, total water may have equaled 730 ml. per kilogram. The question arises as to whether some patients with this disease have a low total body chloride and extracellular volume relative to total body water, irrespective of heat stress. If so, an increase in cell hydration might aggravate pulmonary and cardiac difficulties, in addition to those related to high environmental temperatures.

The data obtained from the muscle analyses of 4 children who died from fibrocystic disease of the pancreas are recorded in Table II. These data are compared with the normal values for the age in question, as provided by the work of Metcoff and col-

leagues.[112] These observations predict loss of extracellular volume and sodium chloride content in the muscle and gain of cell water. The problem is worthy of further study.

In studies of kwashiorkor, Trowell, Davies, and Dean[113] emphasized that in the absence of complete anorexia, vomiting, diarrhea, and pyrexia dehydration is present, for which there is no obvious explanation. Moreover, dehydration is associated with hypotonicity of body fluids. In the early stages of malnutrition, oliguria with a lack of thirst is the rule which eventually gives place to polyuria, and the urine is then hypotonic to plasma. Widdowson and McCance[114] found that malnutrition was usually associated with a relative increase in extracellular volume and a deficiency of tissue potassium. Metcoff and others[115] studied the serum electrolyte concentrations and the composition of muscle and skin in malnourished Mexican children. They found that in severely malnourished or atrophic children without frank edema there was a significant lowering of the serum sodium and chloride concentrations. There was a tendency to metabolic acidosis with the pH values ranging from 7.24 to 7.47. Frequently the serum potassium concentration was also low. Analysis of tissue revealed that there was an increase in the total content of water, sodium, and chloride, and tissue potassium tended to be low. This was true in patients who appeared dehydrated. The findings illustrate that clinical observation may not always interpret correctly the actual changes in body composition.

Metcoff and others[115] found that expansion of extracellular volume occurred only in malnourished children who had advanced to the atrophic stage. Indeed, the chloride space of muscle was significantly low in some examples of malnutrition, and there was an increase in the intracellular fluid volume, if known fluid or electrolyte losses were to some extent associated. Conditions thought to be separate entities, dystrophy, kwashiorkor, athrepsia, and the like, appeared to be stages in a single, continuous, and progressive process.

CENTRAL NERVOUS SYSTEM DISEASE AND EXTRACELLULAR VOLUME

The finding of hypernatremia or hyponatremia in the plasma of the patient with central nervous system disease can provide the clinician with a serious puzzle. Concomitant changes in extracellular volume occur. Hypernatremia and central nervous system disease are usually associated with loss of water and some contraction of extracellular volume. Loss of water in the unconscious patient can occur from deprivation due to the fact that thirst mechanisms are nonoperative in the unconscious state.[116] Also, neurological lesions can interfere with the normal sensation of thirst, even in the conscious state.[117, 118, 119] Second, cerebral lesions may lead to destruction of normal antidiuretic activity and thus to diabetes insipidus. Third, in tube feeding of the unconscious patient there is the danger of loading the patient with protein and producing a profound osmotic diuresis and water depletion.[120]

Hyponatremia in central nervous system disease is usually associated with retention of water in the extracellular phase, as shown by the use of bromide some years ago.[1, 2] In bacterial meningitis an excessive content of body water relative to sodium and chloride can arise. In a 3-month-old infant[1] with meningococcal meningitis and a serum sodium of only 114 mEq. per liter the corrected bromide space was significantly reduced in the face of a normal volume of body water. Work in progress shows that salt loss with extracellular volume loss is not unusual in bacterial meningitis of infancy. Twitching or convulsions occur. Nyhan and Cooke[121] studied the problem and drew attention to the occurrence of water intoxication in conditions producing inflammation of the central nervous system. There is an increase in cellular and extracellular fluid volume. Augmentation of antidiuretic activity is probable; the situation is correctible with hypertonic saline.

In tuberculous meningitis, however, the problem is different.[1, 2] There is clearly

hypotonic expansion of the extracellular fluid (plasma sodium, 120 mEq. per liter or less, corrected bromide space high), but here total body water is most often low. In 6 out of 11 patients with tuberculous meningitis, the total water was less than normal on a weight basis.[2] Therefore there is loss of water from the cellular compartment. On occasion the total water is high on a weight basis, but here, I believe, malnutrition and long periods of poor intake of food may enter into the picture. Such malnutrition lowers body weight and body fat and consequently there is a relative increase in total water per unit of weight. Hence, in long-standing tuberculous meningitis, it is wise to think of extracellular volume as a fraction of total body water. By so doing weight changes due to malnutrition will not lead to false interpretations of the status of body water.

In a 1-year-old infant admitted recently to this hospital with tuberculous meningitis, and with only a 1-week history of illness, the weight was 9.1 kilograms, total water only 420 ml. per kilogram (low), and corrected bromide space 260 ml. per kilogram (slightly above normal). Extracellular volume was 62 per cent of total body water instead of the expected 47 per cent. Total water was reduced but this reduction was due to cell water subtraction and not to any loss of extracellular volume. Unlike the other forms of bacterial meningitis, the change in volume and concentration of extracellular fluid occurs in every patient with tuberculous meningitis.

Why should this biochemical lesion arise? Crawford and associates[122] demonstrated an expansion of extracellular volume in infants with severe allergy to cow's milk. This expansion occurred at the expense of cellular water. Hypotonicity was noted. Perhaps the biochemical lesion in tuberculous meningitis is due to allergy. The same biochemical lesion arises in generalized tuberculosis,[1] and allergy is a prominent feature in the pathogenesis of tuberculosis. The demonstration of this biochemical lesion is a helpful diagnostic aid.

It was suggested in previous work[1] that the antidiuretic hormone played a part in the production of hypotonic expansion of the extracellular fluid in central nervous system disease. McCrory and Macaulay[123] gathered important evidence from a patient with a cerebral lesion supporting this contention. Schwartz and co-workers[124] suggested that an inappropriate secretion of antidiuretic hormone occurred in various conditions of chronic disease. Fourman and Leeson,[125] however, gave injections of Pitressin to patients with cerebral disease and hypotonic expansion of the extracellular fluid and did not note an impressive increase in urine concentration. They suggest that, when the extracellular volume is expanded beyond a critical limit, Pitressin (or endogenous antidiuretic hormone) no longer acts at the level of the kidney. The underlying mechanism responsible for extracellular retention of water is not clear.

True cerebral wasting of salt,[126] with a definite brain lesion, loss of extracellular volume, and a prolonged sodium wasting, is usually confined to elderly patients[127] and is not well documented in the pediatric literature.

EXTRACELLULAR VOLUME AND VOLUME RECEPTORS

From a consideration of conditions in which a change of extracellular volume is characteristic, it becomes clear that many factors are involved to some extent in the maintenance of this volume or "steady state." The integrity of renal function, posterior pituitary and adrenal functions, thirst mechanisms, nutritional intake, and metabolism are all concerned. In the discussion of neonatal problems and again during consideration of changes of volume in central nervous system disease, allusion has been made to the possibility that change in extracellular volume, per se, can set mechanisms in motion. Thus it would seem that there are receptors in the body that are sensitive to change in extracellular volume. It would seem fitting to conclude this dissertation on this theme.

In 1909 Starling[128] suggested that the renal excretion of salt and water must be

conditioned by the volume of the body fluids as well as by their composition. Peters[129] in 1935 wrote that one of the factors controlling sodium excretion was some function of the blood volume. Homer Smith[130] has recently reviewed the subject of volume change and its effect on water and sodium excretion. Only brief mention can be made here. Distention of the left atrium and proximal parts of the pulmonary veins leads to a water diuresis[131] and it would seem that the afferent nerve fibers are carried centrally by the vagus. It must be presumed that such neural pathways can also inhibit the neurohypophyseal system and suppress the output of antidiuretic hormone. This mechanism is now referred to as the Henry-Gauer reflex.

Leaf and coauthors,[132] Weston and others,[133] and Cheek and West[134] showed that under conditions of excessive hydration with expansion of extracellular volume, there is eventually a prominent and well-defined loss of sodium chloride (natriuresis) that can precipitate salt depletion. Presumably another receptor in the interstitial or extracellular fluid is at work with similar neural pathways and hormone effects. In our own experiments, large doses of desoxycorticosterone did not prevent the natriuresis,[134] and we were disinclined to the view that a fall in circulating mineral corticosteroid was the entire explanation for it. On the other hand, it was thought that the renal nerve supply might act as an efferent pathway from some "receptor."

Although denervation of the renal arteries was found to reduce, even abolish, the response in dogs, some of the control dogs in which the kidneys were exposed, but not denervated, also showed a reduced response. These observations would not seem worthy of mention, if Bricker and colleagues[135] had not found that the kidney transplanted from one twin to another demonstrated satisfactory renal function in all respects except for response to expansion of extracellular volume. The natriuretic response was not recorded and they concluded that the renal nerve supply might serve as an efferent pathway.

Bartter and associates[136] have evidence that the thyroid-carotid artery junction is the locus where change in volume will cause an increase in aldosterone secretion, whereas stimuli mediating a decrease are transmitted by the vagus nerve.

The secretion of aldosterone is intimately related to the volume of extracellular fluid as emphasized by Bartter and co-workers.[137] The work of Denton, Goding, and Wright,[138] involving the transplant of the adrenal gland into the neck of sheep, showed that the aldosterone response of the adrenal is independent of the sodium concentration of the blood perfusing the gland, is independent of the nerve supply to the gland, but is related to the volume of extracellular fluid. Contraction of volume leads to an increased output of aldosterone. It would seem that secretion of aldosterone is under the influence of a volume receptor which regulates its output by means of a humoral mechanism. Yankopoulos and others[139] produced evidence, by means of cross circulation experiments in dogs, that such a humoral mechanism exists. Farrel's work[140] suggested that a humoral mechanism exists in the diencephalon and in the area of the pineal body. This structure represents the vestige of a third eye. As stated in a recent editorial,[141] "It would be fitting if it were confirmed that this structure is concerned with 'seeing' that the salt content, and hence the volume of extracellular fluid of the body, are maintained within normal limits."

SUMMARY

1. Extracellular volume is an important parameter of the body. Extracellular fluid surrounds the tissue cells and has a high chloride and low potassium concentration. Extracellular fluid is comprised of interstitial fluid (36 per cent), connective tissue water (35 per cent), and plasma, bone, and gastrointestinal water (29 per cent). Extracellular volume closely approximates, biochemically and morphologically, under physiologic conditions the volume of the corrected chloride space. The chloride space is defined as the volume of distribution of chloride in the

body having a net concentration of chloride equal to that of a plasma ultrafiltrate (120 mEq. per liter). When this chloride space is corrected for chloride outside the extracellular fluid (red blood cell and visceral cell chloride), the resulting volume approximates true extracellular volume. Evidence is presented that 10 to 13 per cent of chloride is intracellular, and 10 per cent is taken as the correction factor. The chloride space can be conveniently measured with stable bromide since the distribution of these anions in the body is almost identical.

2. Data are presented on extracellular volume from the first day of life up through childhood. During the first year of life the volume comprises 47 per cent of total body water and during the second year 41 per cent. Chemical maturity is then reached and this relationship alters less noticeably with further maturation.

3. At various age levels the relation between extracellular volume and the volume of glomerular filtration per day is almost linear. The turnover of extracellular fluid through the glomerular membrane is greater in the infant than in the adult (maximum at 18 months).

4. Basal metabolic rate is linearly related to the volume in the older child and adult, but in the infant there is less fluid for each basal calorie. Since metabolic functions are accelerated in early life, the reserves of extracellular fluid at this time may be inadequate, particularly if "stress" supervenes and metabolism is raised further.

5. From a consideration of the differential growth equation, evidence is presented that during growth a change in the mathematical relationship between body weight and extracellular volume occurs at about 5 kilograms in weight (6 weeks of age). It was known that the growth equation for total chloride and body weight in the fetus and newborn infant changed to a new equation at about that period.

6. Mention is made of pathologic changes in extracellular volume during early life, including some aspects of adrenal, renal, and gastrointestinal disease. Changes in volume due to malnutrition are discussed, and attention is drawn to fibrocystic disease of the pancreas, where evidence is presented that the volume is reduced in terms of total body water. Muscle data indicate that the sodium and chloride content is decreased in the disease.

7. Change in extracellular volume and sodium concentration in central nervous system disease are reviewed and the suggestion is made that the biochemical lesion seen in patients with tubercular meningitis is related to allergy. A brief note concerning "volume receptors" is included.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS was the first Children's Hospital Medical Center admission of a 9 11/12-year-old white boy, with complaints of intermittent exertional cyanosis and anorexia, of one month's duration.

Physical examination when he was first seen was unremarkable except for pallor. His symptomatology abated for a while; his temperature never went above 100° F.

Approximately 2 weeks prior to admission, the youngster was seen by his family pediatrician. At this time, a rather striking precordial systolic murmur was noted. The temperature was 98° F. and pulse 96 per minute. Erythromycin, 200 mg. every 24 hours, and Bicillin were given. He seemed to improve and was started on oral penicillin, 200,000 units three times daily. A week before admission he was found to have a hemoglobin of 7.5 Gm. per cent, and a white blood cell count of 7,600 per cubic millimeter. During the week prior to admission he complained of intermittent malaise and anorexia, and had a temperature varying between 99° and 101° F. He was admitted for evaluation.

A heart murmur was noted early in childhood. There was no history of cyanosis or exertional cyanosis until the present illness, and he had participated in full activities at school and at home.

On admission the temperature was 100.2° F., pulse 125 per minute, and respirations 35 per minute. Blood pressure in the right arm was 125/70, and in the right leg 170/110 mm. Hg. He weighed 62 pounds and was 54 inches tall. He was a fairly well developed and well nourished child, in chronic distress, but he appeared quite alert. The skin had a pinkish hue. The lips and nail beds were grossly cyanotic. There were no petechiae. There was no evidence of infection in the oral cavity. The chest was barrel-shaped, with some increase in the anteroposterior diameter. The heart appeared large to percussion. The point of maximum cardiac impulse was in the left lower sternal border in the supine position, and at the nipple in the upright position. There was a Grade III systolic murmur, heard best along the left sternal border and well transmitted to the apex, the axillae, the neck, and the back. No definite diastolic murmur was heard. P_2 was louder than A_2 and no definite splitting

was heard. The liver was enlarged and was not pulsating; it filled the entire epigastrium and extended approximately 5 cm. below the costal margin. The spleen was hard and palpable 4 cm. below the costal margin. No tenderness was present. Marked clubbing involved fingers and toes. There were good femoral pulses. The neurological examination was within normal limits.

On laboratory examination, 3 urinalyses were obtained. All showed specific gravity greater than 1.020. On one occasion there was a 2-plus albuminuria. The second time this was normal. On one examination the sediment showed 2 to 4 red blood cells. There was no evidence of casts or white cells. The initial hemoglobin was 7.5 Gm. per cent. The red cell count was 2.65 million. Calculated total blood volume and plasma volume were 63.8 and 30 ml. per kilogram of body weight, respectively. The white cell count was 6,700, with 79 per cent polymorphonuclear leukocytes, 5 per cent bands, 22 per cent lymphocytes, and 3 per cent eosinophils. The platelets appeared decreased on smear. Blood type was Group O, Rh positive, with negative Coombs test. The nose and throat cultures did not show any significant pathogen. The stool guaiac was 1 plus on only one occasion. The prothrombin time was 15 seconds (65 per cent normal). Serum iron was 119 gamma per cent. Sickle cell preparation on blood was negative three times. The liver function tests were normal except that there was a 3-plus cephalin-cholesterol flocculation, and the indirect bilirubin was 1.4 mg. per cent; the total serum bilirubin was 1.7 mg. per cent. The total protein was 6.73 Gm. per cent. Febrile agglutinations were negative. Chest x-ray revealed a heart of normal size and contour. The lung fields were normal. Electrocardiogram was essentially normal. Mechanical fragility and the incubated osmotic fragility of erythrocytes were both increased. The barium swallow suggested esophageal varices. Normal bone marrow contained decreased platelets.

The child had a low-grade fever throughout his stay, but was never in acute distress. Upon exertion he definitely became blue and dyspneic. He was seen in consultation by several members of the staff who concluded that this possibly could be old rheumatic heart disease with complicating subacute bacterial endocarditis. However, 3 blood cultures were negative. The youngster was subsequently discharged, to be followed as an outpatient.

He was readmitted 4 months later.

In the interim, he had been at the House of the Good Samaritan for study and convalescence. He was found to have a progressive anemia, leukopenia, and thrombocytopenia. Congenital hemolytic anemia was ruled out and steroid therapy was used ineffectually in an effort to raise the platelet count. The following results were obtained by cardiac catheterization of the right heart: mean pressures were: right atrium 6 mm. Hg; right ventricle 13 mm. Hg; pulmonary artery (rest) 14 mm. Hg; pulmonary artery (exercise) 18 mm. Hg; brachial artery pressure 120/65 mm. Hg. Flows were: systemic 9.0 and effective pulmonary 4.9 L. per minute per square meter. Resistances (dyne-sec. cm.$^{-5}$) were: pulmonary 65, systemic 700.

Fig. 1. Wide tortuous shadows indicate esophageal varices.

Pulmonary function studies performed after admission were within normal limits. However, the patient became markedly cyanotic and dyspneic when he ran upstairs. At rest, the arterial oxygen saturation was 86 per cent, with mild exertion 63 per cent, and after pure oxygen for 10 minutes, 96 per cent. Angiocardiography, performed by dye injection into the left brachiocephalic vein, was normal.

Laboratory data and findings of physical examination were unchanged.

An operation was performed. Following this, the child did rather poorly and died.

DR. ABRAHAM M. RUDOLPH.* Of the large amount of information given on this patient, there are two outstanding problems which, if we can explain them, will probably lead to the correct interpretation of this illness. These are: cyanosis and clubbing, and probable portal hypertension.

Is there a cardiac basis for the cyanosis? If so, the abnormality is most unusual since pressures in the chambers of the right heart are normal. With right-to-left intracardiac shunts, leading to cyanosis at the right ventricular level, right ventricular pressures of about systemic magnitude are necessary and, if the shunt occurs between the atria, distinctly elevated right atrial pressures would be required. Most commonly, too, there would be some evidence of pulmonary arterial and/or right ventricular hypertension. There are a few situations where right-to-left shunts occur with nearly normal pressures at the atrial level: these include Ebstein's anomaly of the tricuspid valve and anomalous drainage of a systemic vein into the left atrium such as a persistent left superior vena cava or an anomalous inferior vena cava. Perhaps x-rays will help at this point.

DR. E. B. D. NEUHAUSER. First, x-rays of the skull show a large cranial vault, which we interpreted as evidence of arrested hydrocephalus. A spot film of the barium swallow shows irregular filling suggesting esophageal varices (Fig. 1). Routine x-ray of the chest shows a heart within the upper limits of normal size and contour, with clear pulmonary fields and no accentuation of bronchovascular markings. There is a series of films from angiocardiographic examination.

Fig. 2. Angiocardiogram during phase of filling of peripheral pulmonary vessels.

DR. RUDOLPH. The normal cardiac silhouette tends to exclude Ebstein's anomaly, which usually has a rather characteristic bulge on the right side. These films of the angiocardiogram show radiopaque medium passing from the veins of the left arm into the right atrium and right ventricle, thus eliminating a persistent left superior vena cava. Often, in a study of this type, reflux filling of the inferior vena cava from the right atrium will be evident. This was not observed in this case, so that we cannot tell from the examination whether or not the inferior vena cava drains normally to the right atrium, or abnormally into the left atrium. Angiography or dye dilution studies via one of the veins of the leg would have helped to exclude this latter possibility.

*Dr. Rudolph was Associate in Pediatrics, Harvard Medical School, and Associate Cardiologist in Charge of the Cardiopulmonary Respiratory Laboratory, The Children's Hospital Medical Center, Boston, Mass. He is now Associate Professor of Pediatrics, Albert Einstein College of Medicine, New York, N. Y.

Later films of the angiocardiogram demonstrate normal filling of the pulmonary arteries and pulmonary veins in sequence, thus providing no evidence for the existence of a large pulmonary arteriovenous fistula (Fig. 2). At the same time, we note that the left atrium and ventricle do not appear greatly enlarged. The absence of left atrial and ventricular enlargement, the absence of left ventricular hypertrophy on electrocardiogram, and the relatively late onset of cyanosis lead me to exclude anomalous entry of inferior vena cava to left atrium. An extracardiac origin of the cyanosis has yet to be excluded.

First, were abnormal hemoglobins present?

DR. SHERWIN V. KEVY. Spectrophotometric analyses of hemoglobin gave normal results.

Fig. 3. Organ block. The flabby, dilated, and hypertrophied heart lies between the lungs, which show prominent pleural markings (above). The liver (middle) has been tipped upward (left side of picture) to reveal partly sectioned undersurface. The coarsely nodular appearance is easily seen. The splenorenal venous anastomosis (lower right, above kidney) is patent and can be traced to portal vein and inferior vena cava (behind portal vein). The kidneys are large and pale.

DR. RUDOLPH. The fact that the lungs appear normal on x-ray, and angiocardiography, and that pulmonary function studies were normal, excludes conventional pulmonary causes for the cyanosis. Now we know that the arterial oxygen saturation rose from 86 per cent at rest, to 96 per cent on breathing oxygen. Perhaps this helps to exclude a respiratory cause of the cyanosis since, often, with oxygen breathing the oxygen levels will rise to 100 per cent. Measurement of plasma-dissolved oxygen may be useful in differentiating pulmonary from cardiac cyanosis. Oxygen dissolved in plasma rises normally under such testing to levels of 1.6 to 2.0 volumes per cent. In cardiac cyanosis or actual shunting of blood, this value is lower.

Was the plasma oxygen content determined?

DR. KEVY. There is no record of this.

DR. RUDOLPH. Of the unusual types of pulmonary cyanosis, that which is associated with large arteriovenous shunts has already been excluded by x-ray. The data we have do not, however, exclude the possibility of multiple small (even microscopic) intrapulmonary arteriovenous shunts. Probably we should refer to these tiny passages as shunts and reserve the term "fistula" for the large, clinically demonstrable shunts.

Finally, can the cyanosis be associated with some other factor? We do know that cyanosis occurs in hepatic disease, especially when advanced portal hypertension is present; this introduces the patient's second problem, namely, portal hypertension. This derangement, together with its cause, may account for almost all the clinical features described: hepatomegaly, splenomegaly, low grade fever, slight hyperbilirubinemia, esophageal varices, and hypersplenic picture of pancytopenia. Also, we can recognize other features of the case. The very high cardiac output may be a result of several mechanisms. Anemia of 7.5 Gm. per cent hemoglobin, the hypoxia (demonstrated by the arterial oxygen saturation of 86 per cent),

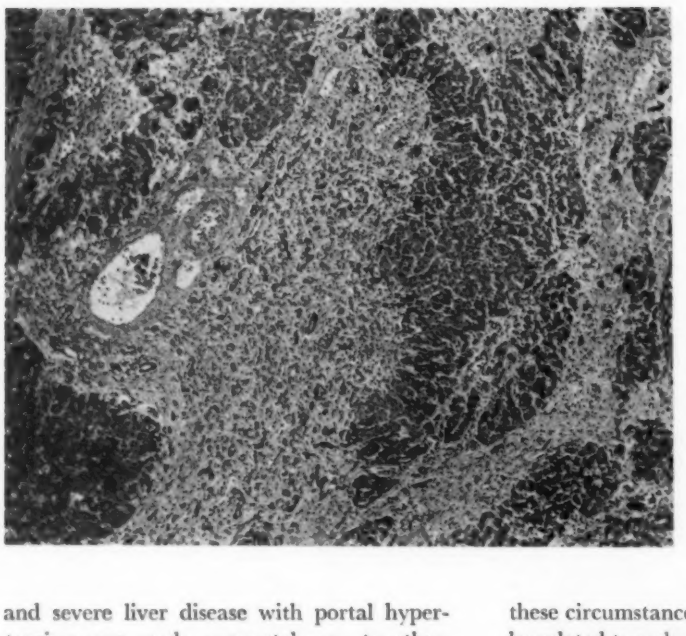

Fig. 4. Heavy scars intersect masses of hepatic parenchymal cells. The area of ductular proliferation (center) follows from the margins of a previous massive necrosis. (Hematoxylin and eosin. Original magnification ×120.)

and severe liver disease with portal hypertension can each, separately or together, contribute to high cardiac output, and could explain the heart murmurs.

Abelmann and colleagues[1] have considerable data indicating that with hepatic cirrhosis and elevated cardiac output there is increase in peripheral blood flow with opening up of peripheral arteriovenous shunts, with such gross manifestations as "liver palm" and development of "spider nevi." The data of Shorr and co-workers[2] would indicate that in liver disease there may be a failure to destroy certain circulatory vasodilator substances (VDM).

Several hypotheses have been advanced to explain the occurrence of cyanosis associated with portal hypertension. First, there is a shift of the oxygen dissociation curve of hemoglobin to the right—that is, the saturation of blood with oxygen is lower with the same oxygen tension than in the normal individual. Just why this should be is not completely clear. We probably cannot completely explain the cyanosis in this patient on the basis of deficient oxygenation of blood associated with very high cardiac output and anemia since response to oxygen breathing should be better under these circumstances. Next, could the cyanosis be related to pulmonary arteriovenous shunts, similar perhaps to those developing in the peripheral circulation? It has been claimed that such potential shunts exist normally in lung tissue and we know they have been demonstrated in diseases which destroy pulmonary parenchyma, such as bronchiectasis. Similar shunts have been demonstrated by postmortem injection techniques in one patient who died with cyanosis, cirrhosis, and portal hypertension.

Much more likely, however, is the development of some type of portal to pulmonary venous communication. Calabresi and Abelmann[3] at autopsy injected the portal system of patients with cirrhosis and portal hypertension. In 2 of 19 patients they demonstrated portal to pulmonary venous communications. It may well be that in such individuals there is a reopening of the normal potential channels existing between portal and pulmonary veins which are usually closed during embryologic development.

Third, in the normal individual there are communications between bronchial veins, pulmonary veins, and systemic veins. Dr. Auld, and others working in our laboratory, have shown, in the dog, that because of

normal pressure differences, the flow in these veins is from pulmonary to systemic veins.[4] We have been able to show that when systemic venous pressure rises sufficiently, this direction of blood flow is reversed from systemic toward pulmonary veins. With portal hypertension we know that elevated pressures may be transmitted via esophageal varices to mediastinal veins, and so probably then through bronchial veins. In the dog which anatomically has only small venous communications, very large reversal of venous blood flow may be demonstrated in this way, up to 20 ml. per minute having been observed.

Studies of blood ammonia levels in cirrhotic patients provide some evidence favoring this interpretation since arterial concentrations of ammonia are actually often much higher than concentrations in venous blood. One explanation of this might be direct flow of portal blood to the arterial circuit at the pulmonary level.

Finally, then, I think that this boy's problems all revolve around the fact that he had portal hypertension. I cannot really distinguish the exact cause of the portal hypertension, whether presinusoidal with malformation of portal vein, parasinusoidal from direct hepatic abnormality, or postsinusoidal, relating to hepatic vein obstruction. The cyanosis, I believe, is largely related to development of vascular shunts, just which and where would be difficult to say, but probably the most important would be from portal vein, to mediastinal vein, to bronchial veins—and so to the systemic circulation. I think that the operation consisted of a splenectomy with splenorenal shunt.

Dr. Charles A. Janeway. In this patient the liver is quite large and biochemical abnormalities are relatively mild. This may not be the usual picture of atrophic cirrhosis with portal hypertension. Nor do we have the large liver and jaundice of biliary cirrhosis. Would these facts make one lean toward obstruction of hepatic venous outflow, perhaps related to an anomaly of the inferior vena cava at or above the hepatic level?

Dr. Rudolph. Early in many processes leading to a contracted cirrhotic liver, the liver is enlarged and even at this stage, portal hypertension may exist, whereas ascites becomes somewhat more common as the liver shrinks down in size and becomes increasingly scarred. Measurable biochemical disturbances in hepatic function may also not become prominent until the disease is very far advanced, indeed.

As to the question of congestive hepatomegaly, as in some form of subacute or chronic Chiari syndrome, there is no history of an acute episode which weighs against but does not exclude such a process. Anomalous entry of inferior vena cava into the left atrium might possibly be complicated by hepatic disease but does not fit too well, as noted before.

Dr. Alexander S. Nadas. I agree with Dr. Rudolph's analysis of this case and would definitely exclude anomalous inferior

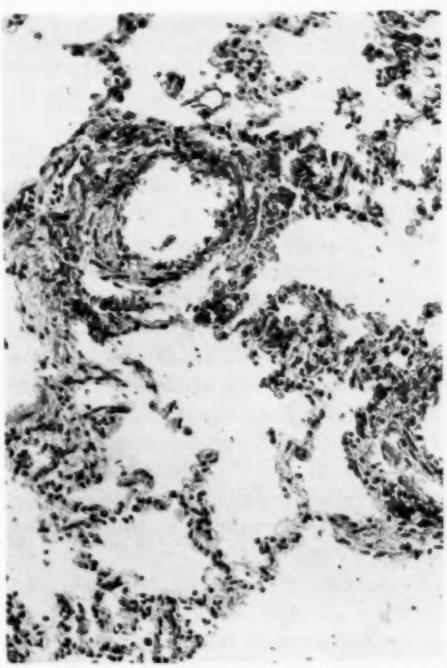

Fig. 5. Dilatation and intimal sclerosis of a pulmonary arteriole. (Hematoxylin and eosin. Original magnification ×130.)

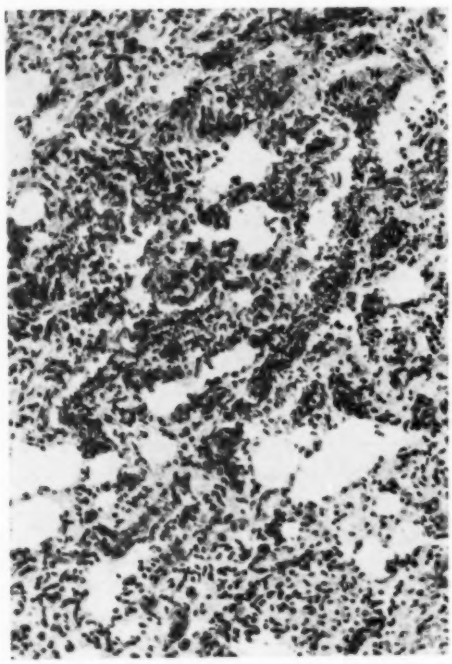

Fig. 6. Groups of unusually dilated alveolar septal vessels can be traced on serial sections to pulmonary vein and to the typical pulmonary arteriole. (Hematoxylin and eosin. Original magnification ×150.)

vena cava in the absence of left-sided cardiac enlargement. Very likely, then, the rather loud cardiac murmur is related to the anemia. Perhaps the murmur heard in infancy was functional and unrelated to the present one. Another point: if subacute bacterial endocarditis superimposed upon old rheumatic valvulitis was seriously considered during the first admission, 3 negative blood cultures have not ruled this out. All of us have treated cases of bacterial endocarditis which could not be diagnosed bacteriologically. Perhaps this diagnosis was not so seriously entertained as the protocol would indicate.

I would think, as Dr. Rudolph does, that there is a shunt of desaturated blood but I am not sure at what level, or that it will be anatomically demonstrable.

Dr. Gordon F. Vawter. Just how big was the liver? Some of these patients hyperventilate and one wonders if the viscera could have been pushed down by overdistended lungs.

Dr. Kevy. Drs. Nadas, Massell, and Haggerty agreed with us that the liver was very large.

Dr. Hardy Hendren. On the second admission the liver appeared somewhat decreased in size over what had been noted previously.

Dr. Vawter. We now show his clinical appearance on his first admission, in 1954. He has a peculiar, puffy, almost feminine appearance.

Dr. Stanley M. Wyman. When I first saw the patient just prior to referring him here, the most outstanding findings were the hepatosplenomegaly and anemia. I wondered whether or not he had bacterial endocarditis, superimposed on some type of congenital heart disease, and so sent him here. It might be of interest to know that the rest of the family, as I briefly knew them, were all well and without known diseases.

Dr. Hendren. At the time of operation there was no ascites, but the liver was coarsely nodular and cirrhotic. The enlarged, hard spleen was removed and a splenorenal venous anastomosis was performed. Postoperatively, blood pressure could not be maintained; sensorium remained clouded, and he died about 18 hours after operation.

Dr. Vawter. The liver was coarsely nodular, with heavy deep scars and large, fleshy, mostly regenerative nodules (Fig. 3). The liver was about 100 Gm. under the expected weight for age, principally associated with atrophy of the left lobe. Microscopically there was a combination of collapsed fibrotic lobules and regenerative masses of cells (Fig. 4). The picture is that of *postnecrotic scarring of the liver,* which may arise as a result of exposure to toxins, viral infection, and, possibly, even certain metabolic derangements. The portal venous obstruction is, then, intrahepatic. There is aneurysmal dilation of the portal vein and massive congestive splenomegaly, in this instance associated with extramedullary hematopoiesis, perhaps partly reflecting the anoxemia. The spleno-

renal shunt was widely patent and competent at the time of autopsy (Fig. 3). The heart was twice overweight, dilated, and quite flabby, as might be expected in anemia, with superimposed circulatory failure (Fig. 3). There were no septal defects or valvular abnormalities in the heart.

Shunts of venous blood to the left side of the circulation, namely, to the left atrium, were demonstrated at three levels, but which of these were most important cannot be distinguished.

First, abdominal venous channels bypassed the liver through the gastrosplenic ligament to adjacent diaphragm, and thence to mediastinum.

Second, an unusually prominent vein ran up the anterior abdominal wall, through the anterior mediastinum into the drainage area of the bronchial veins.

Third, serial microscopic sections of the lung demonstrated arterioles with intimal sclerosis (Fig. 5) such as may follow high pressures which lead into almost angiomatous congeries of dilated vessels (diameters of 100 μ are common) and thence to pulmonary veins, so that microscopic pulmonary arteriovenous shunts were present (Fig. 6).

Other changes consist of an overweight megalencephalic brain, of uncertain cause but showing microscopic evidence consistent with hepatic encephalopathy.

The kidneys show the so-called glomerulosclerosis which may be associated with chronic hepatic disease.

The postoperative collapse may well be related to fairly extensive acute necrosis of the liver, suggesting that the hepatic circulation was already marginal by virtue of the cirrhotic process, and the stress of surgery tipped the balance toward an irreversible lesion.

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COMMENTS ON CURRENT LITERATURE

Recent findings concerning viremia in the human subject

THE role of viremia in human infections has not been completely clarified. Although in a considerable number of instances viral agents have been recovered from the blood, such isolations have not figured prominently in the diagnosis of virus diseases. In the mosquito-borne encephalitides, however, viremia is considered of real epidemiologic significance, and the presence of virus in the peripheral blood plays an important role in arthropod transmission. Under certain epidemic conditions man appears to be the source of virus for arthropod vectors, as in sandfly fever, dengue, and urban yellow fever. In equine encephalomyelitis horses do not appear to develop a high titer of virus in the blood; according to some epidemiologists this titer is not sufficient to infect mosquitoes with any degree of regularity. By contrast, relatively high titers of virus have been detected in the blood of chickens and wild birds, especially nestlings. In all the species tested, viremia was transient, lasting for a period of several days only, and brought to an end by the appearance of neutralizing antibodies. On occasion equine encephalomyelitis viruses and similar strains of virus have been recovered from the blood of human patients during life.

In the case of St. Louis encephalitis, the virus has rarely been isolated from human body fluids. During epidemics and in interepidemic periods, cases of this disease have been identified mainly by suggestive clinical manifestations confirmed by the demonstration of increasing antibody titer during the course of clinical recovery. One such interepidemic case in the St. Louis area[1] was of special interest. A filtrable agent identified as the virus of St. Louis encephalitis was recovered from the peripheral blood of an 8-year-old boy whose clinical manifestations were suggestive of a virus infection with minimal central nervous system involvement. During the course of clinical recovery the patient developed increasing titer of antibody to the newly isolated virus, and to known strains of St. Louis encephalitis virus. This child resided in a wooded suburban area, and had evidence of numerous mosquito bites at the time of hospital admission.

A recent report from Panama[2] describes the isolation of strains of St. Louis encephalitis virus from forest mosquitoes being trapped in Darien province, and from the blood of 2 fieldworkers who were suffering from a mild clinical infection. Both had been engaged in field studies in this region and were regularly exposed to mosquitoes in the course of their activities. Both of these workers experienced a febrile illness with clinical evidence of mild central nervous system involvement, and both developed during the course of clinical recovery type-specific humoral antibody to the St. Louis virus. The isolated strains were identified readily as belonging to Group B, according

to the classification of Casals and Brown.[3] Cross-challenge and mouse protection tests showed the strains to be distinct from yellow fever and Ilhéus viruses. Detailed complement-fixation tests carried out at the Rockefeller Foundation Virus Laboratories confirmed the identification that these strains belonged to the St. Louis type.

Following the finding of poliomyelitis virus in the blood of monkeys and chimpanzees fed virus-containing food, or experimentally infected by other routes, a search was made for poliovirus in the blood of human patients.[4] In these early attempts the virus was detected very infrequently, which led to the conclusion that "the presence of poliomyelitis virus in the human blood stream is not a common event."[4] With the improved isolation techniques available in recent years, however, viremia can be demonstrated more readily.[5] Virus in the blood stream associated with exposure to the polioviruses may be more common than has been supposed, since its presence does not necessarily result in detectable signs and symptoms.[5-7] Viremia in clinical case contacts, as in household or other close contacts without clinical signs of disease, has been described in a number of recorded instances.[8] As early as 1952 Horstmann[9] showed that poliovirus was present in the blood of all 4 children in one family with known exposure. Three of the children had minor illness and one remained asymptomatic. Except in rare instances the virus has not been recovered from the blood of poliomyelitis patients who show clinical paralysis. However, in one recorded case viremia was demonstrated in a patient who had extensive paralysis at the time that the blood specimen was obtained.[10]

More recent demonstrations of viremia in the human subject concern the isolation of virus from the blood in Coxsackie B meningitis and in ECHO virus infections, including a case of aseptic meningitis, ECHO Type 9 virus. In 1957 Shelokov and Habel[11] reported the isolation of Coxsackie B_2 virus from the serum of a patient 3 days after the onset of a febrile illness, but 5 days prior to the onset of clinical meningitis. The patient was a physician engaged in virus research who became ill while investigating an outbreak of disease characterized by fever and dizziness, chest pain, myalgia, and nuchal discomfort. His activities in connection with the disease outbreak included examination of patients, collecting and testing of blood, pharyngeal, and fecal specimens, some of which were found to contain Coxsackie B_2 virus. In the case of the physician, Coxsackie B_2 virus was recovered repeatedly by tissue culture from a specimen of serum obtained 5 days prior to the onset of meningitis. This virus was isolated also from stool specimens obtained during the prodromal phase and during convalescence. Increase in antibody titer to the virus was significant. In a discussion of the clinical and laboratory findings in this case, the authors emphasized the need for further information as to the importance of viremia in relation to pathogenesis, stating that it "is quite possible that every systemic infection with the Coxsackie B viruses is accompained by viremia."[11]

Viremia during the course of infection with various strains of ECHO viruses has been reported in a few cases: ECHO Type 16 early in the course of Boston exanthem[12]; Type 9 recovered from the blood of 2 patients, one 36 hours before, and the other 24 hours after, the onset of illness.[13, 14] In experimental infection in chimpanzees viremia could be demonstrated 24 hours after ingestion of Type 4 ECHO virus, but was not isolated from the blood after the ingestion of Type 6.[15] It has been suggested[16] that if viremia is a feature of infection with the enteroviruses such as ECHO and Coxsackie, it probably occurs early in the prodromal period as is thought to be the case with the polioviruses. In a recent publication, Yoshioka and Horstmann[16] report the investigation of an institutional epidemic of infection with Type 9 ECHO virus. Fifty-seven resident children, 6 to 12 years of age, experienced clinical symptoms ranging from mild febrile illnesses to aseptic meningitis. By tissue-culture isolation of virus from

rectal and throat swabs and by serologic studies, it was evident that virtually all the children in this building of the institution were infected. Viremia was detected as early as 6 days before onset of fever in some cases. In one patient with aseptic meningitis, ECHO Type 9 virus was isolated from the blood 3 days before the onset of fever, and 5 days before central nervous system signs developed. Likewise, from a spinal fluid sample obtained one day after the onset of meningitis in this patient, ECHO Type 9 virus was recovered. The investiagtors state that "the pattern of isolation from the blood, throat, and fecal specimens of infected persons is similar in infections with Type 9 ECHO virus and poliovirus, and suggests a similar pathogenesis of disease associated with these two enteric agents."[16]

Such studies as these, correlating clinical observations with laboratory and investigative findings, including antibody titers, will contribute to a better understanding of the pathogenesis of virus disease, particularly in relation to problems dealing with immunity.

RUSSELL J. BLATTNER, M.D.

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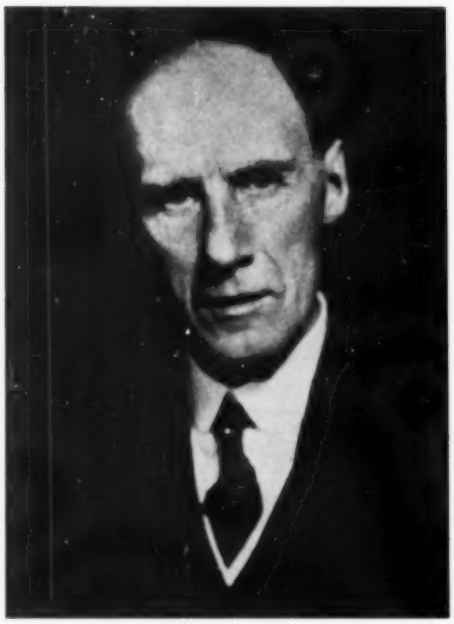
PEDIATRIC PROFILES

Sir Robert Hutchison, Bart.

(1871–1960)

MY FIRST contact with Robert Hutchison was when I became his resident at The Hospital for Sick Children, Great Ormond Street, on Jan. 1, 1925. He was then approaching his middle fifties, absolutely in his prime, and I find it difficult to believe that I am older now than he was then. He was a tall, rather gaunt person, with baldness already well advanced, dressed usually in a long gray "morning coat" style. He arrived at the Hospital on the stroke of 10 A.M. on Mondays and Thursdays, and together we went round his ward of thirty-odd beds, along with the only medical registrar (senior resident who did not reside!) and about ten to fifteen students, either girls from the Royal Free Hospital or visiting postgraduates. The child in the first bed presented him with a pink carnation. Histories had to be succinctly given and then he would examine the essential part of the child, comment on the diagnosis, and speak about treatment. His speech still carried a Scottish accent even after many years in London and he spoke beautifully with a terse, often scathing style. Although he had married a woman doctor he never quite approved of women medical students, and his whole training and experience had been so essentially based on clinical examination with a minimum of essential laboratory support that at that time, 35 years ago, he did not approve of x-ray examinations either and pictures had to be hidden! The design of the ward was such that he approached every patient from the right side, and for this reason his palpation of the pyloric region for a possible tumor in a baby was not very satisfactory. "A tumour that you can only feel from one side of the bed is not a tumour at all," was one of his remarks when I faintly remonstrated. However, I then tried turning the babies round with the head at the foot of the bed and after this he took the hint! Looking back I realize that I was more privileged than many because of my Scottish name and ancestry. The morning round would end about 11:30 A.M. and then his excellent and tolerant ward-sister and I would seek a place to sit down and discuss the gross errors we seemed to have committed. I learned so much from him in the 6 months of the post; he was always my favorite among my chiefs and teachers.

He was born in 1871 in the Midlothian county in Scotland, the scene of Walter Scott's novels, and although his parents were not poor his early life was far from pampered (a word he freely applied to certain children in later years). He graduated from the famous Edinburgh University Medical School with the highest honors in 1893. After resident appointments there, including a resident post at the Sick Children's Hospital, and visits to Strasburg and



Sir Robert Hutchison

Paris, he was appointed to a junior position in the department of chemical pathology at Edinburgh. Then he descended on London —like many Scots before and since—and there he stayed for the rest of his active life. He became a junior resident at The Hospital for Sick Children, Great Ormond Street, and after a further period as a physiologist at the London Hospital Medical School he was appointed to the visiting staff at Great Ormond Street in 1900. The same year he was also elected to the staff of the London Hospital as a physician, where he looked after adults as well as children. He already had published his first book, *Clinical Methods,* and the same year that he secured his permanent hospital posts he produced his famous *Food and the Principles of Dietetics.* His popular *Lectures on Diseases of Children* followed in 1904. There had also already been several scientific papers. It was clear then, as it remained throughout his career, that he had the gift of writing as well as of speaking, and if a teacher is born, not made, then Hutchison had this lucky gene.

He was a prolific writer. A hand list of his publications compiled in 1951 for a celebratory number of the *Archives of Disease in Childhood* on the occasion of his eightieth birthday by Dr. A. White Franklin gave 276 references to books, articles, lectures, and letters in the medical press. He was a great simplifier and this explains his attitude on infant feeding, which he spoke about with abundant common sense and clarity. He was an early advocate of cod-liver oil as a supplement for bottle-fed babies. Langley Porter has recorded in the same birthday number referred to that when Hutchison's experiences with this substance were reported to the American Pediatric Society they were received "politely but dubiously." Two years later, when Heiman and Grulee presented to the same Society a paper on cod-liver oil in the prevention of rickets, it is recorded that John Howland rose in wrath to protest at such "nonsense," but it drove him to test the theory. Later his work with McCollum and Simmonds led to the isolation of fat-soluble vitamins. I mention this episode to illustrate how far and wide Hutchison's influence ranged. I think among his pupils he is the most quoted authority, and seldom a teaching session passes without my using one of his helpful remarks.

A busy consulting practice, his hospital work, lectures to learned medical societies, books to be revised (and more to be written) comprised a full life for Hutchison. He married in 1905 and there were three sons and one daughter. One of the sons was studying medicine at Oxford when he succumbed to a dissecting-room infection. I was working at Great Ormond Street at the time and I greatly admired the way he took this blow. He was happy in his family and in his family holidays. I do not know what sort of father he was when his children were young. He always denounced overfussy and adoring parents. When his daughter had her first son I remember a visit to Robert in retirement: I had to listen

to a long exposition of this wonderful baby's virtues! So he was human after all! Indeed, behind a stern appearance and a caustic tongue there were a warm heart and great kindness.

Distinctions naturally came his way. He received honorary degrees at Edinburgh, Oxford, and Melbourne. He held office at the Royal College of Physicians of London and was President from 1938 to 1941. This was naturally a restricted period in the activities of the College and many of us regretted that he had not had a time of peace in which to make his wisdom and guidance better felt.

I think he lived too long to be entirely happy at the way things were going in the pediatric world. Despite his early interest in chemistry he was scornful of "all this pH stuff." He had little use for preventive medicine in general terms, although as indicated above he realized how a proper diet might prevent specific diseases. At my last visit a few years ago he was worried about the influence of the United States upon British medicine! He thought we were becoming too dependent. "Too many American books are being reviewed in British journals." But I am glad he lived so long, and I shall miss his talk, especially the warning introduction "My dear-r-r" with rolling r's that presaged my name before the criticism came after a suitable pause. He did very much indeed for pediatrics.

ALAN MONCRIEFF

Correspondence

To the Editor:

In the August, 1960, issue of The JOURNAL OF PEDIATRICS, pages 190 to 203, there is a paper by McGann and Carter entitled "The effect of hemolysis on the van den Bergh reaction for serum bilirubin." The authors state that hemolysis in serum samples results in decreased azo bilirubin color development and hence in measured bilirubin levels which are falsely low. They also state that no adequate explanation for the effects of hemolysis on the van den Bergh reaction could be found.

In early 1960 when working on a comparison of methods for serum bilirubin determination I found the same effect of hemolysis. If heparinized blood is added to a plasma sample from exchange transfusions, the azo bilirubin color* is decreased with increasing amounts of blood in the sample. Thus, with the Malloy and Evelyn method, the plasma diluted 1/10 with water, the degree of reduction after 60 minutes (when full color development may be expected) was 4 to 9 per cent in 8 different experimental series when the sample contained about 35 mg. hemoglobin per 100 ml. and 53 to 76 per cent when the sample contained about 1,400 mg. hemoglobin per 100 ml. With the same method but with the plasma diluted 1/31 with water the corresponding figures for reduction of color after 30 minutes were 9 to 10 per cent and 37 to 62 per cent, respectively. With the Jendrassik and Grof method (the plasma diluted 1/10) the figures were 4 to 11 per cent and 11 to 35 per cent, respectively.

Possible explanations for the phenomenon are technical error, destruction of bilirubin, or disappearance of azo bilirubin color. I have studied these alternatives and have found that with the Malloy and Evelyn method when the sample contains blood, the addition of methanol destroys part of the bilirubin before the azo bilirubin has been formed. After addition of blood there is also some degree of azo bilirubin disappearance, "fading," in this method. The fading causes less reduction of the bilirubin values measured than the destruction of bilirubin. In the Jendrassik and Grof method the main effect is a fading of the azo bilirubin color. This fading can be totally prevented by addition of ascorbic acid before alkalizing the sample. The amount of ascorbic acid used is the same as that used by Nosslin in his Jendrassik and Grof modification for direct reacting bilirubin.[1]

Full details of this investigation will be published later.

MAGNUS MICHAËLSSON
DEPARTMENTS OF PHARMACOLOGY AND PEDIATRICS
UNIVERSITY HOSPITAL OF UPSALA
UPSALA, SWEDEN

**In the following, the 2 isomeric azo pigments formed by the diazo reaction with bilirubin are called azo bilirubin.*

REFERENCE

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News and notes

The University of Texas Postgraduate School of Medicine announces a postgraduate seminar on **Current Management of Diabetes Mellitus** to be held January 15 at the Texas Medical Center, Houston. The faculty will consist of Dr. Priscilla White, Boston; Dr. Holbrooke Seltzer, Dallas; and Dr. C. W. Daeschner, Galveston.

For further information write to Office of the Dean, The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Building, Texas Medical Center, Houston 25.

Dr. William Curtis Adams, former Assistant Professor of Child Health at the University of Louisville School of Medicine and Chief Pediatrician of the Louisville General Hospital, has been appointed Medical Director of Variety Children's Hospital, Miami, and Associate Professor of Pediatrics at the University of Miami School of Medicine.

A course on **Pediatric Neurology,** a seminar on the nervous system in childhood, is offered to specialists in neurology and pediatrics May 22 to 26, 1961, at Columbia University College of Physicians and Surgeons. The fee is $100.00.

For further information write to Melvin D. Yahr, M.D., Assistant Dean, College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.

Dr. Jerome Glaser, Rochester, New York, was honored by the Section on Allergy of the American Academy of Pediatrics at the Chicago meeting last October with a scroll in recognition of his contributions in the field of pediatric allergy.

The Pediatric Department of Memorial Hospital for Cancer and Allied Diseases announces their annual course in **Pediatric Oncology** for pediatricians, general practitioners, and health officers to be held April 26 to 28, 1961. The faculty will include 20 members of the Attending Staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. The class is limited to 15 and the fee is $35.00. For information contact Chairman, Department of Pediatrics, Memorial Hospital, 444 East 68th Street, New York 21, N. Y.

Applications for charter membership in the **American Society of Diagnostic Radiology** are being received. Membership is open to cardiologists, chest physicians, gastroenterologists, rheumatologists, orthopedists, pediatricians, otolaryngologists, internists, and general practitioners who do or may desire to do diagnostic radiology in their offices. For further information write to Louis Shattuck Baer, M.D., F.A.C.P., 411 Primrose Road, Burlingame, Calif.

The American Board of Pediatrics, Inc., certified the following diplomates at Chicago, Illinois, Oct. 21 to 23, 1960:

Agee, Betty Austin, 2634 West 112th Street, Inglewood 4, California
Agee, Richard Bryan, 2634 West 112th Street, Inglewood 4, California
Alexander, Margaret Neill, 122 South Hickory St., Escondido, California
Arthur, James Hartford, 4401 East Yale Avenue, Denver 22, Colorado
Boehm, John Joseph, 1280 Humboldt St., Denver 18, Colorado
Boehnke, Henry L., 1705 East Main St., Medford, Oregon
Borofsky, Leatrice G., 1352 Reservoir Avenue, Roslyn, Pennsylvania
Bradley, Jeanne B., 6820 Creston Road, Minneapolis 24, Minnesota
Bruns, W. Theodore, 8430 West Capitol Drive, Milwaukee 22, Wisconsin
Bugbee, Lawrence Myers, 4401 East Yale Avenue, Denver 22, Colorado

Caudill, George Gray, 520 39th, Des Moines, Iowa

Coldwell, James G., 1004 North McKinley, Sand Spring, Oklahoma

Conard, Patricia, 1928 Kennicott, Des Plaines, Illinois

Crittenden, I. Hunter, 233 Cajon St., Redlands, California

Doyle, John Henry, 163 Medical Arts Bldg., Louisville 17, Kentucky

Flood, George William, 527 Gordon Street, Corpus Christi, Texas

Free, Julianne, 141 West Ocean Boulevard, Long Beach, California

Galevi, Osman, 3041 Eastmoreland Drive, Oregon, Ohio

Gans, Ida Henriette, University Hospital, Minneapolis 14, Minnesota

Giammona, Samuel Thomas John, 2120 Emerald Avenue, N. E., Grand Rapids, Michigan

Grant-Johnson, Millicent, 3001 North Inyo Street, Bakersfield, California

Greiner, Robert A., Mill Road, Adrian, Michigan

Griesbach, Peter H., 202 Clover Avenue, Edgebrook Heights, McHenry, Illinois

Hayes, James W., 61 Robinson Road, Severna Park, Maryland

Heckman, Donald C., 214 East Broadway, Owatonna, Minnesota

Hempel, Dean J., 1610 West Lake Street, Minneapolis 8, Minnesota

Hogan, William J., 250 North Ottawa Street, Joliet, Illinois

Hoyt, C. Sherman, 4809 West 60th Street, Minneapolis 24, Minnesota

Huber, Robert Bernard, 716 North Spring Street, Elgin, Illinois

Jarvis, Roy J., 605 Midfield Drive, Kingsport, Tennessee

Jelks, Mary Larson, Department of Pediatrics, University of Florida Hospital, Gainesville, Florida

Johnson, John Leslie, 1500 San Pasqual, Pasadena, California

Katkov, Harold, Children's Medical Group, 5830 Overhill Drive, Los Angeles 43, California

Kavanagh, Aidan Joseph, 710 Canada Building, Saskatoon, Saskatchewan, Canada

Kempton, George B., 748 Crescent Road, Jackson, Michigan

Kindrachuk, William, 2917 Clements Avenue, Detroit 38, Michigan

Kuhn, Paul LeRoy, 31 South Eaton Court, Denver 26, Colorado

Libo, Hersh William, 142 Coleridge Street, Brooklyn 35, New York

Lucas, Robert Theodore, Jr., 1350 Kings Drive, Charlotte 7, North Carolina

Lynfield, Joshua, 35 Carman Avenue, Cedarhurst, New York

Mark, John S. T., 1079 "B" Street, Hayward, California

Mebane, William Nelson, III, 308 West Springfield Avenue, Philadelphia 18, Pennsylvania

Meechan, Robert John, Doernbecher Hospital, 3181 S. W. Sam Jackson Park Road, Portland 1, Oregon

Michels, Max I., USAF Hospital, Chanute Air Force Base, Illinois

Moore, Tom D., 78th Hospital, ADC, Hamilton Air Force Base, California

Moorhead, Samuel Roscoe, Jr., 226 Moultrie Square, Anderson, South Carolina

Morton, Kathleen Cameron, Box 637, Kennewick, Washington

Nakamura, Frances F., 1481 South King Street, Honolulu, Hawaii

Neeno, Katsumi, 500 West Milwaukee Street, Janesville, Wisconsin

Newton, Gwendolyn G., 303 Grove Avenue, Barrington, Illinois

Nickey, Laurance Noyes, 4312 O'Keefe, El Paso, Texas

Nutting, Helen M., 1047 Somerset, Grosse Pointe Park 30, Michigan

Paulissen, James P., 949 Glenview Avenue, Wauwatosa 13, Wisconsin

Perucca, Leo G., 804 West Springfield Avenue, Champaign, Illinois

Pinto, Peter S., 502 Torrance Boulevard, Redondo Beach, California

Pyne, Gordon E., 4575 Sand Point Way, Seattle 5, Washington

Quie, Paul G., 2154 Commonwealth, St. Paul 8, Minnesota

Ratner, Harold, 1776 Union Street, Brooklyn 13, New York

Robinson, Janice Yvette, 5781 Carson Road, St. Louis 40, Missouri

Rogers, William B., Jr., 1935 Second Street, Cuyahoga Falls, Ohio

Schafer, Thomas L., Grand Forks Clinic, Grand Forks, North Dakota

Scherz, Robert Grover, 130th Station Hospital, APO 403, New York, New York

Schuman, Stanley H., 1427 East Park Place, Ann Arbor, Michigan

Sommer, Donna Meddaugh, 5457 South University Avenue, Chicago 15, Illinois
Steiker, Daniel D., 325 Dartmouth Avenue, Swarthmore, Pennsylvania
Sternfeld, Jack, 4801 Church, Skokie, Illinois
Stickles, Lee E., 361 Regent Street, Fredericton, New Brunswick, Canada
Swaiman, Kenneth Fred, 4123 Meadowbrook Lane, St. Louis Park, Minnesota
Trumpour, Donald J., 414 Main Street, Rochester, Michigan
Ushkow, Martin Charles, 107 Robbins Lane, East Syracuse, R. D. 3, New York
Vernie, Rudolf, 609 North Anderson Street, Ellensburg, Washington
Wagner, George R., 3610 South Sunset Drive, Milwaukee 20, Wisconsin
Walker, Norma Bragg, 3601 Chapman Highway, Knoxville 20, Tennessee
Weisberg, Israel, 2103 Adelbert Road, Cleveland 6, Ohio
Westlin, William Frederick, Jr., 8-A Troy Drive, Springfield, New Jersey
Wilson, John R., 1033 West Fulton Street, Grand Rapids, Michigan

Special Foreign Certificates:

Chan, Asteria C., 133 Baco, Quezon City, Philippines
Cheung, Che-Sun, 7 Village Road, Happy Valley, Hongkong
Reyes, Araceli R., Memorial Medical Center, Williamson, West Virginia
Sangkam, Poonsri, 131 Rongmaung Soi 4, Bangkok, Thailand
Sarinas, Teresita J., 380 Dolores, San Francisco 10, California

Erratum. *The article, "Teratogenesis with cancer chemotherapeutic agents" by Russell J. Blattner, M.D., Alice P. Williamson, B.A., Lydia Simonsen, M.D., and G. Gordon Robertson, Ph.D., in the February, 1960, issue of the Journal, page 285, should have carried the footnote, "Supported by United States Public Health Service Grant No. CY-3057."*

EDITOR'S COLUMN

The parenteral fluid therapy of diarrhea: regimens reconciled

HISTORICALLY, it can be said that the most recent chapter in the evolution of fluid therapy began in 1945 when, through the efforts of Darrow, potassium deficiency and the importance of its correction were first recognized.[1] In the ensuing fifteen years, our ability to treat abnormalities in electrolyte metabolism has greatly improved but, at the same time, the subject has in many respects become more complicated. As with all new advances in complicated fields, research on potassium metabolism was intense in the years after it came into prominence and large segments of meetings were devoted to papers and discussions by the "salt and water" boys. The excitement has now subsided, and most of the returns are in. It should, therefore, be possible for the practitioner who has neither the time nor the facilities to make a hobby of problems of this sort, but who often sees a good many dehydrated patients in the course of his practice, to have at hand regimens of fluid therapy management, applicable to the various types of dehydration, which are relatively simple, foolproof, and free of complications.

Viewed in this light, the paper by Smith and Etteldorf[2] comparing, on a series of 56 patients, three of the more popular fluid regimens for the therapy of diarrhea fills a need. They chose to study a modification of the regimen advocated by Hartmann, and the more recent Butler-Talbot and Darrow regimens. There are several points of similarity among these three plans. All use about the same volume of fluid for the initial rehydration of the infant and the same total volume on the first and second days of treatment. The amount of free water included in each is approximately the same. The points on which they differ lie principally in electrolyte composition. The total amounts of sodium and potassium administered during the first day of therapy, the ratio of sodium to potassium, and the amount of lactate administered all differ considerably among the three procedures.

The Butler-Talbot regimen, distinctive in providing the least amount of lactate and the greatest amount of potassium, was the slowest in correcting the acidosis and caused the greatest elevation in serum potassium. Several infants receiving this regimen were still in rather marked acidosis after 24 to 36 hours of therapy and, because of this, some were given supplementary sodium lactate. The modified Hartmann regimen, by which large amounts of sodium lactate and small amounts of potassium are given, rapidly overcame the acidosis but often resulted after 36 hours of therapy, in an elevated carbon dioxide content and pH and a low serum potassium level. There was some tendency also for edema to occur in patients receiving this regimen, but this may have been coincidence. The regimen described by Dar-

row was intermediate between the other two in the amounts of sodium, potassium, and lactate administered. It corrected the acidosis in 36 to 40 hours without overshoot and serum potassium levels stayed within the normal range. In administering this regimen, the K-lactate solution was given subcutaneously as originally described by Darrow. This use of subcutaneous fluids constituted, in these authors' hands, a disadvantage of the method; the other regimens, supplying fluids only by the intravenous route, were technically easier to administer. As for clinical manifestations of complications of fluid therapy with the three regimens, only edema and persistent hyperpnea of acidosis, as mentioned above, were observed; symptoms of water intoxication and tetany were not observed, and hypo- and hyperkalemia, although present, were not manifested either electrocardiographically or clinically.

In summing up, the authors felt that there was merit in the rapid correction of acidosis afforded by the Hartmann regimen but at the same time recognized its disadvantages, i.e., second-day alkalosis and hypokalemia. With modifications in the direction of reducing the amount of sodium lactate and increasing the amount of potassium, they felt that these disadvantages could be overcome, making it the regimen of choice. Results with Darrow's method were also recognized as satisfactory; the authors could only suggest that it be modified to allow a little more rapid alkalinization and, by inference, to eliminate the administration of fluid subcutaneously.

If one calculates the electrolyte intake for the first day which would obtain for the remodification of the Hartmann regimen suggested by Smith and Etteldorf, one finds that the intake with respect to sodium and potassium would be very similar to the Darrow regimen as used by them and also to a regimen derived from that of Darrow which has been used successfully at Cincinnati Children's Hospital for a number of years. The main difference as will be mentioned below is in the ratio of the intake of chloride to that of lactate. Disregarding for the moment this difference, the similarity of these three regimens with respect to sodium, potassium, and volume of fluid and the good results which all three give in the therapy of the acidosis of diarrhea lead one to feel that despite admitted gaps in our knowledge of the factors and mechanisms controlling electrolyte balance, it is, nevertheless, possible to outline a simple fluid therapy regimen which will do the greatest good for the greatest number. Obviously any basic plan would have to be modified in the presence of a complicating disease such as severe pneumonia, heart disease, or renal disease; but with the knowledge of the limitations necessary in these situations, modifications are easily made once a basic plan is available.

So that the amounts administered can be applied to a wide range of age and size, they should be expressed when possible in terms of surface area[3] or caloric expenditure.[4] This writer prefers surface area as being a method which is easier to teach, remember, and apply, feeling that the practicality of the system outweighs its fallacies.[5] The following represents a synthesis of the volume and composition of the fluids as used in the three plans mentioned above.

The total fluid administered in the first 24 hours need not exceed 3,600 ml. per square meter of body surface, of which in the aggregate about 1,400 ml. should be isotonic with respect to electrolyte and the remaining 2,200 ml. free water as 5 per cent glucose. All the fluids can be given intravenously. First, to improve circulation and initiate rehydration, 360 to 450 ml. of fluid per square meter should be given by rapid infusion over a 45 to 60 minute period. This may be one half isotonic sodium chloride in 2.5 or 5 per cent glucose as recommended by Darrow or M/12 sodium lactate in 5 per cent glucose as proposed by Smith and Etteldorf for the remodification of the Hartmann regimen. If sodium chloride is used, it may be wise to add additional sodium lactate to the fluids given later if the infant is severely acidotic. (It is our policy, in cases where the carbon dioxide content is 8 mEq. per liter

or less, to increase this level by 5 mEq. per liter by infusion of 20 ml. of M/6 sodium lactate or 0.3 Gm. of sodium bicarbonate per kilogram during the first 6 or 8 hours of therapy.)

After the initial hydrating fluid is infused, there remains to be administered about 3,200 ml. of fluid per square meter of body surface during the remainder of the first 24 hours. Of this amount about 1,200 ml. should be isotonic with respect to electrolyte and 2,000 ml. free water. The 1,200 ml. of electrolyte should contain 145 to 170 mEq. of sodium and approximately 40 mEq. of potassium. The anions of the fluid should be distributed between chloride and lactate. It is on this distribution that the Darrow and Hartmann regimens differ fundamentally. The modified Hartmann regimen would supply approximately two thirds of the anion as lactate, whereas the Darrow regimen supplies two thirds as chloride. This writer feels that a decision in this matter is provided by the fact that the average chloride loss in infants with diarrhea, as measured by Darrow,[6] is of such magnitude as to require that chloride constitute two thirds of the anion. By this reasoning, chloride should be included in the mixture in the amount of 125 to 140 mEq. and lactate in the amount of 60 to 70 mEq. In total then, the intake per square meter in the first 24 hours, if the initial hydrating solution is M/12 sodium lactate, would be 180 to 205 mEq. of sodium, 40 mEq. of potassium, 125 to 140 mEq. of chloride, and about 100 mEq. of lactate. If half isotonic sodium chloride were used for the initial hydration, the values for chloride would be 155 to 175 mEq. and for lactate 60 to 70 mEq. Calcium, magnesium, and phosphorus have not been included in the calculations in so far as there is no unanimity of opinion as to the place of these ions in the therapy of diarrhea.

Electrolyte could be supplied in the above ranges by any one of a number of combinations of commercially available fluids. For example, a mixture supplying 3,200 ml. per square meter of body surface might be composed of 1,600 ml. of Butler's solution,* 500 ml. of lactated Ringer's solution, and 1,100 ml. of 5 per cent glucose. If the mixture could be comprised of only 2 fluids, therapy would be simpler. The following are two such mixtures: One would consist of 2,300 ml. of modified Butler's solution† and 800 ml. of lactated Ringer's solution. In this mixture calories are supplied by glucose in a concentration of 5 per cent in the modified Butler's solution. The other simple mixture would be 1,200 ml. of Darrow's K-lactate solution and 2,000 ml. of 5 per cent glucose in water. This last mixture, used with an initial hydrating solution of one-half isotonic sodium chloride, has in our hands been simple to administer and highly effective therapeutically.

As pointed out by Smith and Etteldorf, the presence of hypo- or hyperelectrolytemia with the acidosis does not require that this fluid regimen be modified. With the pooled fluids approximately 40 per cent isotonic with respect to electrolyte, as they are in the regimen described, there is little danger of convulsions from water intoxication in the infant who is hyperelectrolytemic.

In contrast to the apparent agreement as to the amounts of fluid and electrolyte to be supplied the first day of therapy, the amounts suggested for the second day have wide variation. Certain points can be made, however, which serve as guides. With electrolyte losses during diarrhea of the magnitude described by Darrow,[6] it is obvious that the amount of potassium supplied the first day (40 mEq. per square meter) will be insufficient to replace body stores. Therefore, at least the same amount should be given the second day. The amounts of sodium, chloride, lactate, and water furnished the first day, on the other hand, are calculated as sufficient to restore the losses completely, correct the acidosis, and rehydrate the patient. Hence, on the second day only

*Butler's solution is also designated Solution No. 90. It contains per liter: sodium, 60 mEq.; potassium, 25 mEq.; chloride, 53 mEq.; lactate, 25 mEq.; and small amounts of minor ions.

†Modified Butler's solution is also designated Solution No. 48. It contains per liter: sodium, 25 mEq.; potassium, 20 mEq.; chloride, 22 mEq.; and lactate, 23 mEq.

maintenance or slightly greater than maintenance amounts of these substances need be supplied. Thus one could prescribe per square meter 2,000 ml. to 2,400 ml. of fluid supplying 50 to 100 mEq. each of sodium and chloride, and 30 to 50 mEq. each of potassium and lactate. These amounts would be supplied by 2,000 ml. of the modified Butler's solution described above or by 1 L. of Darrow's K-lactate solution together with 1,000 to 1,400 ml. of 5 per cent glucose. These mixtures would supply potassium and lactate in the ranges given, but with the latter mixture sodium and chloride will be in slightly greater amounts than suggested. It is probable that with all homeostatic mechanisms functioning well, as they usually are on the second day of therapy, slight excesses of these ions will not be harmful.

As a final point it will be recalled that therapy with intravenous fluids is potentially a dangerous procedure and should be well supervised and controlled. With a plan of therapy which is simple and convenient, mistakes are less likely to occur. As a final word, it is well to remember, in attempting to modify a good basic plan of therapy, that restraint in fluid administration is usually less harmful than generosity.

CLARK D. WEST, M.D.

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A pediatric career

SUDDENLY and unexpectedly Mrs. John McK. Mitchell (Eleanor Janeway Mitchell) was stricken at the recent session of the Board (American Board of Pediatrics) in Chicago.

Nora Mitchell was reared, lived, and worked in a medical setting. The daughter of Theodore Janeway, successively head of the departments of Internal Medicine of Columbia and of Hopkins, she trained for a career in nursing but by selection and election became the wife and continuous helpmeet of a practicing pediatrician who was destined later in his career to become the Dean of one of our leading medical schools. Perhaps something of her environmental background can be surmised from the career of her brother, Charles Janeway, at Children's in Boston.

After World War II, Dr. Mitchell undertook the Survey of Pediatric Education which was a part of the National Survey of Child Health Services. Mrs. Mitchell was an active participant. Together they visited each of the medical schools in this country and compiled the data which continue to serve as a standard of reference. Subsequently, when Dr. Mitchell became executive secretary of the American Board of Pediatrics, Mrs. Mitchell continued as a member of the "team." From 1948 she served as administrative secretary to the Board. Much of the

credit for the efficient organization of the Board's activities and for its excellent state at the moment belongs to her.

Perhaps most of all, those of us who served on the Board sensed the depth of her concern for the candidate to be examined and were made the more considerate because of it. If the trying time of the Board examination has become a bit more tolerable for a great many tense candidates, it is so in no small measure because of Mrs. Mitchell's attention to the nuances of the two-hour period. Many a candidate, several thousand of them, are unwittingly in her debt, and many more will be, for the kindly, smooth pattern of operation which she helped to develop.

Such as Nora Mitchell leave a rich heritage. If devotion to ideals and the opportunity to translate them into service make for satisfaction in living, then she has been amply rewarded. And those of us who have been privileged to know her as a co-worker and a friend are the better for it.

W. E. N.